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## TREATMENT OF BURNS WITH CHEMO-THERAPEUTIC MEMBRANES

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AND

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NEW YORK

AND

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The present day treatment of burns, particularly their emergency handling in large numbers of cases under conditions encountered in warfare, leaves much to be desired.

This paper deals with the local treatment of second degree burns, in which by definition the epidermis is not completely destroyed but in which the lesion may involve all the superficial layers down to the stratum germinativum from which the mature epithelium originates. Third degree burns present another problem; obviously if the epidermis is completely destroyed, the wounds must heal by granulation or second intention and therefore probably require some form of grafting.

Most of the widely used methods of treating burns have as their object the formation of an eschar over the burned area beneath which healing and epithelization can take place. This eschar is usually produced by repeated application of solutions of various drugs or drug combinations with the common property of coagulating proteins, e. g. tannic acid, silver nitrate, gentian violet (methylrosaniline). While some of them have bacteriostatic properties, it is necessary to start with a clean uninfected surface adequately prepared surgically if infection beneath the eschar is to be precluded.

Recently, an improvement in this therapy has been made by Pickrell<sup>1</sup> with the development of a water-triethanolamine solution of sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) containing methylcellulose. With this solution no coagulation of proteins takes place. The

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1. Pickrell, K. L.: Personal communication to the authors.

eschar is formed by the precipitated methylcellulose and built up to the required thickness by repeated sprayings. The sulfadiazine reduces the incidence of subescharotic infection.

The objection to all of these methods of treatment is twofold. One is that they require the more or less constant attention of a trained attendant until the eschar is formed; this may take many hours. The other is that in the production of the eschar a certain number of layers of viable epithelium are destroyed; this is amply demonstrated to any one who has tried to remove an eschar from a burned surface only to find a raw bleeding surface or a layer of pus beneath. This is particularly important in the treatment of second degree burns in which the epithelium is not completely destroyed. The rapidity with which epithelization in these second degree burns takes place depends directly on how much viable epithelium remains below the burned surface in the form of unharmed epidermis and hair follicles and the care with which this epithelium is protected.

Petrolatum gauze, either alone or in combination with one of the sulfonamide compounds, comes closer to meeting the requirements of an ideal local application, but this is also time consuming, and if a method of immobilization and sterilization by surgical technic is employed, it becomes even more so. It does not, however, harm surface epithelium, and if gently removed so that there is no tearing of epithelium as evidenced by absence of bleeding, it comes closer to meeting the requirements of ideal local treatment.

In order to make available a standard method of therapy which would allow rapid epithelization of burns by relatively untrained attendants, we have experimented with the method of therapy hereinafter described. In our limited experience, it has proved more suitable to the treatment of second degree burns than any other method that we have used.

Hydrated films were prepared from a hydrophilic cellulose derivative,<sup>2</sup> into which the various chemotherapeutic agents were incorporated. These transparent, thin, light and tough films have the useful property (due to the hydrophilic nature of the plastic employed) of becoming pliable when placed in contact with the moist surface of a burn and of following intimately its delicate contours. Moreover, they adhere closely, remain transparent, permitting observation of the healing process beneath it, and are easily removable by simply sponging with water. If excessive oozing threatens to disintegrate the film, a second or third layer can be applied over the first, thus restoring the strength of the membrane.

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2. The cellulose derivative employed at present is methylcellulose. It is likely that other hydrophilic derivatives would be equally satisfactory. These films are not yet on the market.

Also, by mounting these films on gauze, one can give them additional strength, and they can be made into sheets large enough to encircle the torso of an adult.

In medicating these films we have availed ourselves of the latest findings in the field of chemotherapy. Having made observations indicating that azochloramid may inactivate inhibitors of the action of sulfonamide compounds we used this principle to advantage in our work. Also, the recent findings that the effectiveness of sulfanilamide can be stepped up to nearly equal that of sulfathiazole (2-[*para*aminobenzenesulfonamido]-thiazole) or sulfadiazine by adjusting the  $p_H$  to a slightly alkaline reaction was utilized and thus full advantage taken of the greater solubility of sulfanilamide compared with that of the other sulfonamide compounds. We have clinically experimented with such membranes containing 10 per cent sulfanilamide and buffer, with and without quantities of azochloramid. These films are therefore veritable preformed chemotherapeutic eschars.

Clinically, these membranes have been applied in 10 cases with such exceptional success and have shown such obvious advantages over other methods of therapy for burns that we feel justified in presenting this preliminary report.

These cases represent the last 10 consecutive burns treated in New York Hospital. Five of the patients had severe enough burns to require hospitalization. One of them had several small areas of third degree burns on the dorsum of the ankle, and these areas were not treated with the preformed membrane. In the remaining 5 cases the burned area involved one or more of the extremities, and the patients were treated as ambulatory (table).

The longest elapsed time required for complete healing (such that the patient could actually return to work) was twenty-one days. This occurred in a patient who was burned about the head so extensively that his entire crop of thick hair and his eyebrows were burned down to within a few millimeters of the skin. There were second degree burns of the entire scalp, the face, the ears and the hands. Some difficulty was encountered in applying the membrane to the ears and these areas were slower than the others in healing. This patient required nine days of hospitalization with several plasma transfusions to combat loss of fluids and edema.

The 1 patient with both second and third degree burns required six days to completely epithelize his second degree areas beneath the cellulose membrane and thirty-six days to heal his third degree by second intention.

The 5 patients hospitalized spent an average of seven and six-tenths days in the hospital and required an average of thirteen and two-tenths days for complete epithelization.



*Data on Ten Patients with Burns Treated at New York Hospital*

Patient	Age, Yr.	Sex	Date	Condition	Treatment
1	..	..	4/27	Second degree burns on volar and dorsal surfaces of forearm three days previously treated with tannic acid and S.A.	Débridement; buffered sulfanilamide powder, petrolatum gauze
			4/30-5/1	Raw weeping surface	Membrane applied
			5/2	Healed completely	Membrane removed
2	3	M	4/29	Third degree burns on left foot and ankle and second degree burns on face, dorsum of left leg and left thigh; 48 hours old; infected	Débridement, third degree areas; buffered sulfanilamide, second degree areas; membrane applied
			4/30	No change; clean under membrane	Membrane applied to face
			5/1	Second degree areas completely epithelized	Membrane removed
3	51	M	5/12	Second degree burns on entire face, scalp, neck, dorsum of right hand and left thumb with marked edema of face and right eye	Débridement; membrane applied
			5/13-5/16	Edema subsided on third day; membrane partially disintegrated	Membrane partially replaced
			5/18-5/20	Low grade fever; most of burn healed; few moist areas	Membrane removed; buffered sulfanilamide applied to few remaining moist areas
			5/30	Healed completely	
4	33	M	5/16	Second degree burns on anterior surface of right leg treated before admission with kaolin cataplasms * and petrolatum	Débridement; membrane applied
			5/21	Completely epithelized	Membrane removed
5	37	M	5/27	Second degree burns on entire right foot and ankle; smaller areas on face and right thigh	Débridement; membrane applied
			5/28	Membrane partially disintegrated	Membrane replaced where necessary
			6/5	Almost completely healed except bony prominences	Membrane removed
			6/8-6/13	Practically healed; discharged	Buffered sulfanilamide to few remaining moist areas
6	..	F	6/10	Second degree burn on right thigh, leg and hand	Débridement; membrane applied
			6/11-6/23	Burns healing under membrane; occasionally small portions disintegrated	Membrane renewed over small areas where necessary
			6/19	Membrane removed everywhere; burn completely healed except in two small spots where débridement was not originally carried out	Buffered sulfanilamide to two small moist areas
			6/24	Healed in 14 days; back at work in 11 days	
7	13	F	6/18	Second degree burn on right hand	Débridement; membrane applied
			6/20-6/22	Hand edematous and oozing; membrane partially disintegrated; leukocytic layer formed	Second membrane superimposed; membrane and leukocytic layer removed; membrane replaced
			6/27	Few small infected areas remained	Membrane removed; sulfadiazine powder
			7/6	Almost healed	

*Data on Ten Patients with Burns Treated at New York Hospital—Continued*

Patient	Age, Yr.	Sex	Date	Condition	Treatment
8	37	F	6/19	First and second degree burns on right hand and thumb; no blebs	Petrolatum gauze
			6/20	Large blebs on thumb and dorsum of hand	Blebs opened; débridement; membrane applied
			6/27	Healed completely	Membrane removed
9	2	M	6/21	Second degree burns on palms and finger tips of both hands and right forearm	Débridement; membrane applied
			6/22	Oozing but clean	Membrane renewed where necessary
			6/25	Leukocytic layer formed beneath membrane	Membrane and leukocytic layer removed; new membrane applied
			6/27	Both hands infected; membrane disintegrated; arm healed	Sulfadiazine powder to right; membrane to left hand
			7/6	Left hand healed completely; few areas of granulating tissue remained on right hand	Sulfadiazine powder to right hand
10	2	M	6/23	Bilateral second degree burns on the anterior part of the chest	Débridement; membrane applied
			6/24	Clean	Membrane partially renewed
			6/27	Discharged	
			7/1	Practically healed in 7 days	Membrane removed

\* The proprietary preparation used was essentially the same as cataplasin of Knoll, N. F.

The 5 ambulatory patients required an average of eleven and six-tenths days for complete epithelization. This represents a total average of twelve and four-tenths days for the 10 cases.

Admittedly, in none of these cases was the condition of the most severe type, nor were any of the patients in shock; only 2 of them required plasma transfusions, but on the whole the average length of hospitalization was much shorter than that of 103 patients hospitalized between 1932 and 1941, for whom the average was twenty-five days.

In treating these burns we have used the following technic: When the burn is first seen in the accident room, it is débrided and cleaned with solution of sodium chloride or boric acid or azochloramid and sodium chloride as thoroughly as possible, sterile gloves and towels being used but no anesthesia. All dead skin is removed at the first treatment. Cultures and smears are then taken. The preformed membrane is then applied directly to the raw oozing surface, the tissues being relied on to furnish sufficient moisture for the membrane to adhere.

A dry sterile dressing is then placed over the membrane and held by plain gauze bandage.

For the first three or four days there is a steady outpouring of serum from the tissues. During this period the membrane may tend to disintegrate, sometimes requiring additional layers over it. Occa-

sionally, it has been necessary to remove the eschar completely, and under it can usually be found a soft friable layer of leukocytes enmeshed in fibrin which readily peels off the burned surface, leaving a clean glistening surface beneath; to this a new membrane can readily be applied.

When this layer of leukocytes is examined microscopically, usually only a few bacteria are present, and these when found are frequently



Fig. 1.—Photomicrograph of a leukocytic membrane beneath a chemotherapeutic film.

intracellular. This outpouring of leukocytes may be enhanced by the chemotactic effect of the cellulose membrane or some of its constituents.

No attempt has been made so far to use sterilized preformed membranes, but this can be done and is contemplated. However, daily smears and frequent cultures were taken. The smears usually fail to show bacteria, although cultures invariably show staphylococcus or nonhemolytic streptococcus before, during and after healing has taken place. Occasionally other organisms also are found.

We have routinely taken smears from the most exposed and dirtiest-looking portions of the burned areas and then counted twenty oil immersion fields and averaged the count. If this was above twenty, it was called infinity. The results were then plotted as shown in the example given in figure 2.

After the cellulose membrane is removed, any small moist areas remaining are powdered with buffered sulfanilamide powder, and a dry dressing is applied directly over them. The dressing is removed in a day or two and the application repeated if necessary. However, in most

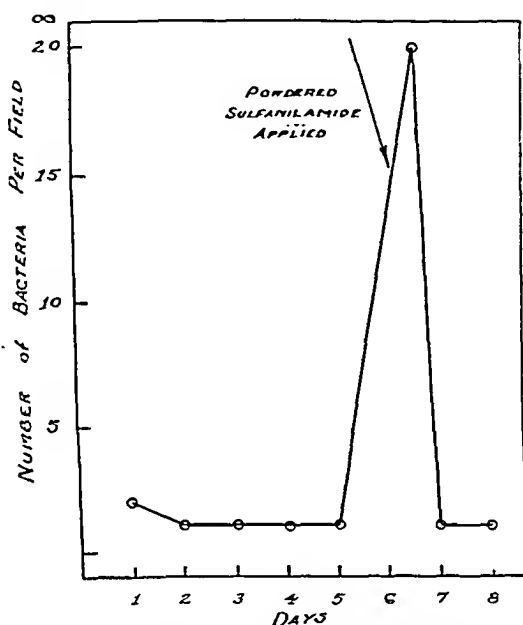


Fig. 2.—Bacterial counts taken on smears from patient 6. The infecting organism was *Staphylococcus albus*. The high count on the sixth day was obtained from a small infected area.

cases a crust forms under which healing takes place rapidly, and no further dressing is necessary.

We have experimented with several different thicknesses of pre-formed eschar but find the thinner ones easier to apply and more readily replaceable.

In 3 cases the sulfanilamide concentration in the blood also was determined. The results indicate that only small amounts of the sulfanilamide have been absorbed. Three determinations yielded 0.0, 0.35 and 0.65 mg. per hundred cubic centimeters. In none of the cases was there any manifestation of toxicity due to sulfanilamide.

Apart from the good clinical results obtained in these 10 cases, the obvious advantages of this form of treatment are its ease and rapidity

of application. Given the sudden incidence of a large number of burns (on board a ship for instance), this membrane can be applied quickly and easily and can be held in the proper position by a dry dressing placed over it. The membrane can be applied by any one trained in first aid. It obviates the necessity of applying ointments, salves or jellies. If it is desirable to remove the membrane, it need merely be moistened with sterile water or solution of sodium chloride. Another practical advantage of this medication is that the material used for it is light and not bulky. A few grams of the membrane replaces bulky and heavy containers. This aspect may be of prominent importance when shipping space is scarce.

NOTE.—Since this report was submitted, 10 additional cases of severe second degree burns have been treated in this clinic by this method. The average healing time in these was nine days, and the patients include a 15 month old child with a burn involving 55 per cent of the surface of the body and a Negro man 21 years of age with 35 per cent of the surface involved. Both were completely healed within twelve days. In the later cases the method employed has been essentially the same as that detailed in the article except for the use of pressure dressings in some cases.

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# GALLSTONE ILEUS

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A series of 6 cases of gallstone ileus at the Salem Hospital from 1938 to 1940 has focused my attention on this unusual form of intestinal obstruction. In the twenty-five years from 1915 to 1940 this diagnosis has been confirmed in 13 cases at the Salem Hospital. This series is one of the largest to be reported from one hospital. Balch<sup>1</sup> listed only 10 cases from the Massachusetts General Hospital, Boston. Likewise, at the Mayo Clinic, Rochester, Minn., Wakefield, Vickers and Walters<sup>2</sup> found only 10 cases. Yet the incidence of intestinal obstruction in these institutions is of course much greater than in the Salem Hospital.

According to the literature, intestinal obstruction is due to a gallstone in about 1 to 2 per cent of the cases. In this series gallstones were responsible in 6 per cent. In 1925 Moore<sup>3</sup> made an estimate of 400 reported cases of ileus due to a gallstone. Since then hundreds of additional instances have been recorded; hence single case reports now have little value unless some unusual feature is present. In recent years much progress has been made in the diagnosis and the treatment of obstruction of the bowel. The reported average mortality of 50 per cent for gallstone ileus is sufficient warrant for the study of a significant group of cases of this condition, from the standpoint of modern diagnosis and treatment.

## AGE

One obvious reason for the high mortality associated with gallstone ileus is the advanced age of the patients. In my series the average age was 66 years. Balch<sup>1</sup> and Borman and Rigler<sup>4</sup> reported an identical average age for their groups of patients. The youngest patient in my series was 50 years old. The oldest, a 79 year old woman operated on by me, recovered from two attacks of gallstone ileus, each necessitating

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From the Surgical Service, Salem Hospital.

1. Balch, F. G., Jr.: Gallstone Ileus, *New England J. Med.* **218**:457, 1938.

2. Wakefield, E. G.; Vickers, F. M., and Walters, W.: Gallstones Causing Intestinal Obstruction, *Surgery* **5**:670, 1939.

3. Moore, G. A.: Gallstone Ileus, *Boston M. & S. J.* **192**:1051, 1925.

4. Borman, C. N., and Rigler, L. G.: Spontaneous Internal Biliary Fistula and Gallstone Obstruction, with Particular Reference to Roentgenologic Diagnosis, *Surgery* **1**:349, 1937.

jejunotomy, and is therefore the oldest recorded patient to survive recurrent ileus. Several authors, however, have listed recoveries from a single episode in patients over 80 years of age.<sup>5</sup>

#### SEX

All authors have found a much higher incidence in female patients, out of proportion to the commoner occurrence of gallstones in women. The ratio is about 5:1. In the 13 cases at the Salem Hospital there was only 1 man.

#### MORTALITY RATE

In the present series the mortality rate was 46 per cent, if 1 non-operative patient is included. This patient had definite, incomplete ileus clinically and roentgenologically at the time of entry into the hospital. A gallstone impacted in the rectum was dislodged digitally. Excluding this case, the mortality rate is 50 per cent, which coincides with an average figure obtained from the literature. Grey-Turner had 8 recoveries in 10 operative cases; in contrast, Möller<sup>6</sup> reported an 89 per cent mortality rate.

#### BILIARY FISTULA

Practically all gallstones which cause ileus are dislodged into the intestines through a cholecystoenteric fistula. The subject of spontaneous internal biliary fistula has recently been reviewed comprehensively by Borman and Rigler. Fistulas of this type are a fairly common complication of long-standing disease of the biliary tract.

In the opinion of most authors an attack of acute cholecystitis subsequent to previous cholelithiasis is often complicated by the intimate adherence of the gallbladder to an adjacent viscus, usually some portion of the gastrointestinal tract. However, many patients give a history of long-standing cholelithiasis only, and in some there is little or no evidence of a previous pathologic condition in the gallbladder. Borman and Rigler expressed the opinion that obstruction of the common duct by a stone in the presence of a patent cystic duct is the initial factor in the formation of a fistula. In 109 cases of biliary fistula described by Bernhard,<sup>7</sup> stones were demonstrated in the common duct of 55 patients. The presence of choledocholithiasis may be demonstrated at operation

5. Turner, G. G.: A Giant Gallstone Impacted in the Colon and Causing Acute Obstruction, *Brit. J. Surg.* 20:26, 1932.

6. Dulin, J. W., and Peterson, F. R.: Intestinal Obstruction Due to Gall Stones—Report of Ten Cases, *Arch. Surg.* 38:351 (Feb.) 1939. Möller, cited by Moore.

7. Bernhard, E.: Die spontanen inneren Gallenfisteln und ihre operative Behandlung, *Dtsch. Ztschr. f. Chir.* 242:493, 1934.

or at autopsy. In 4 of 6 fatal cases of gallstone ileus at the Salem Hospital autopsies were performed. In 2 patients the common duet was extremely dilated and contained many stones. In the remaining 2 the duet was definitely dilated and in 1 instance filled with sandy fluid. It seems a reasonable assumption that obstruction of the common duet is a prominent factor in the production of this fistulous drainage of the biliary tree. It follows that the occurrence of cholecystoenteric fistula may be a life-saving accident, as Dean<sup>8</sup> emphasized, since dilated infected biliary radicles can then be drained into the intestine despite the obstruction of the common duet.

In the large group of 176 cases of cholecystoenteric fistula from the Mayo Clinic, in all of which the condition was due to gallstone ulceration (rather than, for instance, to carcinoma), the sites of the fistulas were as follows: cholecystoduodenal in 101 cases; cholecystocolic in 33 cases; cholecystogastric in 7 cases; multiple in 11 cases.

In 24 cases the gallbladder had ruptured and stones had been discharged into the abdominal cavity. The cholecystocolic fistulas have little bearing on the problem of subsequent ileus, because stones ulcerating into the large intestine are usually defecated uneventfully. In addition to being in the intestinal tract, fistulas have been reported as emptying into the bronchial tree, the pleural and pericardial cavities, the pelvis of the kidney, the gravid uterus and ovarian cysts.

It has been argued that fewer cases of cholecystoenteric fistulas and gallstone ileus will occur in communities in which early operation is frequently performed for acute cholecystitis. It is certainly true that such complications can be largely prevented by earlier operation for the predisposing chronic disease of the biliary tract. It is not easy to determine from the history how often acute cholecystitis is a factor. The symptoms suggesting an attack of acute cholecystitis may closely resemble those due to biliary colic. Likewise, the symptoms which may attend the migration of a stone from the gallbladder to the intestine some months or perhaps years prior to the occurrence of ileus are not unlike those associated with an attack of acute cholecystitis. Case 1 illustrates five characteristic stages in a case of gallstone ileus: (1) antecedent acute cholecystitis; (2) chronic cholelithiasis; (3) the passage of a gallstone through the fistula into the intestine; (4) the recurrent bouts of intestinal colic; (5) the final ileus due to the impacted gallstone.

CASE 1.—A. J., a 49 year old woman, had had postprandial epigastric bloating and tenderness in the epigastrium for four years prior to her first entry into the hospital. In October 1937, two and one-half years prior to her gallstone ileus, she had been hospitalized for three weeks at the Salem Hospital because of an attack of acute cholecystitis. At that time she had had nausea, vomiting, fever

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8. Dean, G. O.: Internal Biliary Fistulas, *Surgery* 5:857, 1939.



and pain in the right upper quadrant of the abdomen. A tender gallbladder was palpated. She had no jaundice. A cholecystogram revealed a nonfunctioning gallbladder. This attack subsided readily, and operation was withheld because of her cardiac condition. She continued to experience epigastric bloating two or three times a week.

Two and one-half months prior to the onset of ileus she experienced a sudden epigastric sensation of "something swelling as though it were going to burst or blow up inside of me." It seems probable that the large gallstone passed into the intestine at that time.

Five weeks before her present entry, her physician thought she had intestinal grip, because of vomiting, diarrhea and periumbilical cramps. This episode lasted

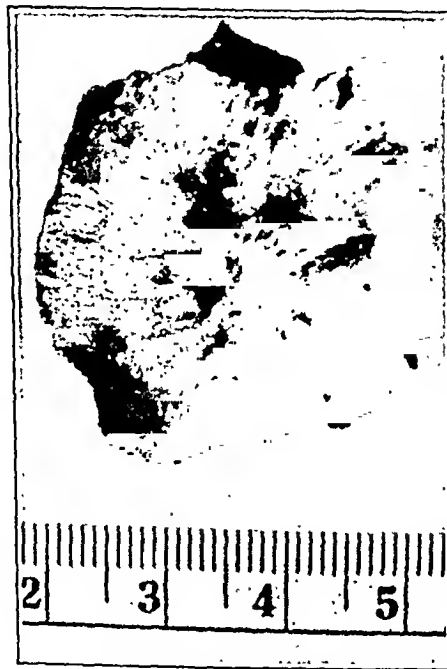


Fig. 1 (case 1).—This huge gallstone impacted in the rectum broke in half during digital removal.

two weeks, and a similar occurrence took place one week prior to entry, with severe midabdominal cramps and vomiting but with no distention.

At her entry, in March 1940, a rectal examination disclosed an impacted gallstone low in the rectum, visualized in the flat plate of the abdomen made on admission to the hospital. The stone broke in half on digital removal (fig. 1).

A cholecystogram showed a nonfunctioning gallbladder. Linear shadows of diminished density in the right upper quadrant of the abdomen suggested gas-filled biliary ducts. An enema of barium sulfate revealed extravasation of the contrast medium from the region of the hepatic flexure into the biliary ducts and thence to the stomach and the duodenum (fig. 2). A diagnosis of cholecystocolic fistula was made. Although operative intervention was not required, the character of the patient's symptoms warranted the diagnosis of actual incomplete ileus. Closure of her fistula was discussed, but in the absence of symptoms of cholangitis the risk was deemed greater than the indication.

In September 1941, eighteen months later, the patient was and had been well except for several chilly sensations. She had had no jaundice, fever or loss of weight, despite her cholecystocolic fistula. She no longer had any indigestion.

Eight of the 13 patients gave an antecedent history suggestive of disease of the biliary tract. Six of them had had an acute episode which may have been acute cholecystitis, but only in case 1 was the evidence sufficient to permit that diagnosis. The remaining 5 people gave no history which implicated the gallbladder. The absence of such



Fig. 2 (case 1).—Cholecystocolic fistula diagnosed roentgenologically with an enema of barium sulfate. The barium sulfate extravasated from the region of the hepatic flexure (through the fistula) into the biliary ducts and thence to the duodenum and the stomach.

a history is not at all uncommon in cases of gallstone ileus, although it seems extraordinary that a fistula could occur without associated symptoms. Case 2 is illustrative:

CASE 2.—Mrs. G. W. T. had had a large ovarian cyst removed when she was 68 years old; at this time a stone the size of a walnut was felt within the gallbladder, which was neither thickened nor adherent. Nine years later the patient

had gallstone ileus requiring jejunotomy, from which she recovered uneventfully. In the intervening nine years she had had no acute or chronic symptoms of disease of the gallbladder.

Whether gallstones which may later obstruct the intestine ever pass into the duodenum via a greatly dilated common duct is controversial. It appears that authentic cases of such an occurrence have been recorded. Many surgeons have encountered an enormously dilated common duct, sometimes reported as resembling a section of small intestine. It is established that passage of large stones may render the sphincter of Oddi incompetent, so that a reflux of gas or barium sulfate through the common duct may outline the biliary tree, thus providing a valuable roentgen finding. The average-sized stone which causes ileus would not pass through the common duct, but many factors in addition to the size of the stone contribute to the occurrence of ileus. Several authors report fatal cases of ileus due to relatively small stones.<sup>9</sup> Cases have been described in which the obstructing stone was thought to have reached the small bowel by way of the common duct, because no fistula could be demonstrated between the gallbladder and the bowel. However, such fistulas may close off completely after the passage of the stone, so that at a later date only dense adhesions mark its site. In 7 of 36 cases of gallstone ileus reported by Courvoisier,<sup>10</sup> in which autopsy was done, no fistulous tract could be found.

#### FISTULA AT AND AFTER THE PASSAGE OF THE STONES

It is not surprising that gallstones lodged in an inflamed gallbladder tend to be extruded through a fistula when one has formed. Progressive shrinking of the entire gallbladder slowly forces its contents into the lumen of the bowel, where free drainage exists. The transit of the stone is occasionally signalized by symptoms resembling those of a stone of the common duct or of acute cholecystitis. Rarely, duodenal obstruction ensues because of a large stone lodged partly in the gallbladder and partly in the duodenum, as in the 10 cases tabulated by Thompson.<sup>11</sup> At times, jaundice and biliary colic attend the passage of the stone due to the proximity of the inflammatory mass to the common duct. The presence of a fistula does not insure the emptying of the gallbladder, as stones are often found in the gallbladder even after one or more have been passed. In Bernhardt's series of 109 fistulas, stones were still present in the gallbladder in all but 17 cases.

9. Wangenstein, O. H.: *The Therapeutic Problem in Bowel Obstruction: A Physiological and Clinical Consideration*, Springfield, Ill., Charles C. Thomas, Publisher, 1937. Borman and Rigler.<sup>4</sup>

10. Courvoisier, L. G.: *Casuistisch-statistische Beiträge zur Pathologie und Chirurgie der Gallenwege*, Leipzig, F. C. W. Vogel, 1890, vol. 12.

11. Thompson, cited by Henry, M. J.: *Gallstones Causing Intestinal Obstruction*, Tr. South. S. A. 44:421, 1931.

When fistulous communication exists between the gallbladder and the upper part of the intestinal tract, further symptoms referable to the fistula may cease once the stones have been discharged or symptoms of chronic cholecystitis may persist. If the gallbladder has drained into the colon, symptoms of cholangitis, namely, chills, fever and loss of weight, are often encountered. In their series of 32 patients with cholecystocolic fistulas, Wakefield, Vickers and Walters found that 19 had recently lost 15 to 40 pounds (6.8 to 18.1 Kg.). These authors commented that it is desirable to operate and close such fistulas because of the frequency of cholangitis and hepatitis. However, a number of authors have



Fig. 3.—This small, shrunken gallbladder emptied directly into the duodenum. The hole in the gallbladder measured 1.9 cm., whereas the gallstone measured 6.5 by 4 cm.

reported cases of cholecystocolic fistula without evidence of ascending infection. In the present series 2 patients had multiple fistulas to the duodenum and the colon for over one year with no symptoms of cholangitis.

Most authors have advised against surgical attack on the fistulous tract after the patient has recovered from gallstone ileus, because of the great difficulty in closing off the opening into the intestine. A great many fistulas close spontaneously. Whether or not this occurs in a particular case is probably related to a patency of the cystic duct. It is often possible to outline the biliary tree because gas or barium sulfate flows through the fistula into the gallbladder and thence to the common duct. If the cystic duct ceases to be patent, the free biliary flush through

the gallbladder ceases. The mucosa of the gallbladder has often been destroyed by the chronic inflammation and ulceration due to the stone. Under such circumstances the gallbladder becomes the blind end of a sinus which tends to close, so that at later operation or necropsy only a dense mass of adhesions may be found. In 3 of the cases in which autopsy was performed such a process was in evidence. In 2 instances the fistulous opening into the duodenum measured 1.5 and 1.0 cm. respectively, whereas stones of a much larger diameter had been removed from the small intestine at operation a few days earlier. In a third case the opening into the duodenum was 1.9 cm. in diameter, whereas the extruded gallstone measured 6.5 by 4 cm. Figure 3 shows the autopsy specimen with the stone held above the fistula.

#### MECHANISM OF BOWEL OBSTRUCTION

Owing to the progress in diagnostic roentgenology, there has been a reversal of opinion with regard to the proportion of cholecystoenteric fistulas to gallstone ileus. In 1890 Courvoisier found three times as many cases of ileus on record as cases of fistula. In 1939 Wakefield, Vickers and Walters studied 176 cases of fistula, among which there were only 10 cases of ileus. It is evident that the majority of gallstones ulcerating into the lumen of the bowel are passed in the stools. Moreover, the presence of biliary fistula must be fairly common and readily discovered if looked for by roentgen examination.

It needs to be emphasized that gallstone ileus is an obturation form of intestinal obstruction (i. e. caused by a loose foreign body within the lumen of the bowel). The gallstone usually commences its downward progress in the duodenum, which is the widest portion of the small intestine. Almost all stones ejected into the colon make their way through the anus without difficulty because of the large diameter of the colon. In the majority of cases the ileum is the site of arrest in the small bowel inasmuch as there is progressive narrowing of the intestinal lumen as the ileocecal valve is approached. Barnard<sup>12</sup> has stated that stones less than 2.5 cm. in diameter are passed spontaneously. However, many factors in addition to the size of the stone influence the occurrence of obstruction. The sharp edges of the stone, kinks in the bowel because of adhesions, the presence of Meckel's diverticulum, a slow rate of peristalsis and ulceration of the wall of the bowel from the trauma of the stones are factors which may precipitate obstruction in cases in which the gallstone is relatively small. In my case of recurrent gallstone ileus, the second episode was caused by a stone smaller than a previously defecated stone.

12. Barnard, H. D.: Intestinal Obstruction Due to Gallstones: Report of Three Cases with Summary of Five More Cases from the Records of the London Hospital, 1893-1901. *Ann. Surg.* 36:161, 1902.

Most writers have expressed the opinion that a stone can enlarge during its stay in the bowel. Wangensteen said that this is especially true if a stone remains in one portion of the bowel for some time during which a medicament, such as bismuth subnitrate, calcium or magnesium carbonate, is taken orally. A number of cases have been cited in which the available evidence suggests that the gallstones had been present within the bowel for years. In a recent case of Clute's, it seems certain



Fig. 4 (case 3).—This patient had multiple gallstones in the ileum for over five years with persistent incomplete intestinal obstruction. Spontaneous closure of the cholecystoduodenal fistula took place.

that the gallstones were present within the small intestine for about five years (fig. 4) :

CASE 3.—H. H., patient of Dr. Howard M. Clute, had had marked loss of weight, nausea and vomiting and had been unable to take solid food for five years. At cholecystectomy only dense adhesions to the duodenum marked the site of the fistula. Subsequently two resections of small intestine were required to remove over a dozen gallstones which were fixed in place in the ileum by multiple areas of constriction of the bowel.

The final arrest of the stone may occur at any level in the intestinal canal. In 6 patients in this study the jejunum was the site of the obstruction, although the terminal part of the ileum is a commoner location. Frequently a temporary halt occurs and is perhaps accompanied by mild obstructive symptoms. Because of ball valve action plus the increased peristaltic effort the standstill may be overcome; symptoms may subside, and downward progress may be resumed. When the stone is finally halted, the block is usually mechanical in nature, and therefore circulation in the bowel is rarely jeopardized until late. The obstruction is not usually a complete one; hence marked distention is not characteristic. Occasionally a sharp stone ulcerates through the intestinal wall; in this event the development of obstruction is related to the associated



Fig. 5.—Three gallstones from the same patient. The upper two caused separate attacks of intestinal obstruction. The bottom one was defecated.

peritonitis. Wangenstein visualized the occurrence of volvulus of the loop of bowel containing the obstructing stone because of the distention and the weight of the proximal loop. Rarely, the obstructive syndrome results from an intussusception with a large fixed gallstone as the leading point.

#### SIZE OF THE STONE

Wangensteen stated that stones large enough to occlude the intestinal lumen are usually at least the size of a walnut. In my series the weights and dimensions of only 5 stones were known. Their average weight was 19.5 Gm. The largest recorded stone was removed successfully from the transverse colon of an 81 year old man by Turner. It weighed 5 ounces (155.5 Gm.) and measured 7 by 6 by 17 cm. Wangenstein pointed out the role of spastic obstruction by calling attention to a stone so small that it weighed less than 4 Gm. yet caused fatal ileus. In my

case of recurrent ileus a defecated stone weighed 13.2 Gm., whereas the stones causing the two bouts of intestinal obstruction weighed respectively 12.7 and 19.0 Gm. (fig. 5).

### SYMPTOMS

In a review of a great many case histories the delay between onset of symptoms and surgical intervention is striking. It is tragic that a form of obstruction of the bowel so readily relieved should be manifested by such indefinite, misleading symptoms with the frequent result of delayed operation. The usual preoperative diagnosis is simply intestinal obstruction on the basis of a history of pain, vomiting and obstipation. However, because of the mechanism of the obstruction, such a history is neither constant nor clear. Symptoms may be correlated with pathologic sequences, viz.: (1) symptoms referable to disease of the gallbladder, usually of long duration; (2) symptoms referable to the emigration of the stone into the intestine from the gallbladder; (3) symptoms pertaining to the current obstruction.

From the majority of patients a history of previous complaints concerning the biliary tract is elicited. Eight of the patients in my series gave such a history, whereas 5 women did not. Sometimes this history is obtainable only after the operation for gallstone ileus, as Colcock mentioned.<sup>13</sup>

When a large gallstone passes into the intestine from the biliary tract, the event may be signalized by a definite bout of severe pain in the upper part of the abdomen and vomiting. However, cholecystitis or biliary colic may also produce similar symptoms. In 2 of our cases it seemed possible from the history to fix the date of transit of the stone. In 1 case this took place four months prior to ileus. In the second case, it occurred one year before and was marked by severe colic and jaundice which quickly subsided.

As the stone makes its downward progress, it characteristically causes cramps. At times temporary ileus with nausea and vomiting occurs. Such episodes may resemble so-called intestinal grip, and this diagnosis had been made in several of our patients prior to the final arrest of the stone. Thus dangerous delay may occur. According to Mast<sup>14</sup> and others such recurrent bouts of temporary obstruction of the small bowel may take place for a year or more prior to the end stage of persisting obstruction. In Clute's case, symptoms of partial obstruction were present for five years.

Rarely, the clinical picture of simple mechanical obstruction may be confused by the complicating peritonitis from perforation. Even

13. Colcock, B. P.: Intestinal Obstruction Due to Gallstones, *Lahey Clin. Bull.* 2:47, 1940.

14. Mast, W. H.: Recurrent Intestinal Obstruction Due to Gallstone, *Am. J. Surg.* 32:516, 1936.



when the stone has come to a final halt, the resultant symptoms are not clearcut as in other forms of obstruction. Colic, nausea and vomiting may be intermittent because of incomplete obstruction. Distention is often not pronounced. Tenderness is not a common finding, since obstruction is purely mechanical at the onset.

Thus the equivocal character of the premonitory symptoms and the actual ileus contribute to the high mortality rate associated with this condition. Many of the patients in my series were not hospitalized until obstruction had been present for several days. The average duration of symptoms prior to hospitalization was two and a half days in those patients who survived and six and three-quarters days in those who died.

#### DIAGNOSIS

The correct diagnosis of gallstone ileus is rarely made prior to operation or autopsy. Lowman and Wissing<sup>15</sup> stated that preoperative roentgen diagnosis of an intestinal obstruction due to a gallstone has been recorded only 11 times. However, the correct diagnosis has been made in addition in some cases in which operation was not performed and in which autopsy later confirmed the roentgen finding. In 1 of my cases (fig. 6), such a diagnosis was advanced by the roentgenologist on the basis of having demonstrated a cholecystoduodenal fistula plus the presence of gas-filled loops of small bowel. The diagnosis by roentgen examination of cholecystoenteric fistula is not uncommon. In this series of 13 cases a correct clinical diagnosis of gallstone ileus was made in 3 instances prior to operation. For 1 woman the diagnosis was obvious, since she had recently passed two gallstones per anum.

In an elderly patient, usually a woman, with a history of disease of the gallbladder, often with repeated episodes, the occurrence of a non-fulminating recurrent obstructive syndrome, with perhaps a shifting focus of symptoms, suggests ileus caused by a gallstone. Such a cause is more to be thought of in those cases in which other commoner forms of obstruction, such as tumor or adhesions, are not suggested. In the history the two commonest features are: (1) the history of chronic disease of the gallbladder, which is obtained in about 50 per cent of the cases and (2) the recurrent character of the obstructive symptoms, which is also true in about 50 per cent of the cases.

Physical findings may be inconclusive. Distention may be only moderate as some gas passes by the obstructing stone. Tenderness is usually a late sign, signifying "weeping" of the dilated obstructed bowel, the development of peritonitis from perforation proximal to the obstruction or a decubitus ulceration through the wall of the bowel at the site of the stone. Irreversible circulatory changes in the wall of the bowel

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15. Lowman, R. M., and Wissing, E. G.: Preoperative Roentgen Diagnosis of Gallstone Ileus, *J. A. M. A.* **112**:2247 (June 3) 1939.

rarely characterize an obturation type of intestinal obstruction until late. A mass is so rarely felt that this sign has little diagnostic value. Powers<sup>16</sup> mentioned that tenderness beneath the right costal margin was suggestive when present.

It is important to distinguish the intestinal colic due to the passage of an irritating foreign body from the colic set up by obstruction of the lumen of the bowel. In a review of a great many case histories, a number of patients were listed who suffered mild colic relieved by the



Fig. 6.—The diagnosis of cholecystoduodenal fistula was made on the presence of this small mushroom-like cavity projecting up from the duodenal cap. Fourteen days later the large gallstone seen in figure 3 was found in the ileum at autopsy.

defecation of a gallstone. Wagner<sup>17</sup> listed 334 cases of gallstone ileus, but 93 of the patients defecated the gallstone. A report from the Mayo Clinic described 176 cholecystoenteric fistulas but enumerated only 10 cases of gallstone ileus. Therefore, we may conclude that gallstones are

16. Powers, J. M.: Acute Intestinal Obstruction Due to Impacted Gallstones: Report of Four Cases, *Surg., Gynec. & Obst.* **28**:416, 1928.

17. Wagner, A.: Ileus durch Gallensteine, *Deutsche Ztschr. f. Chir.* **130**:353, 1914.

often extruded into the intestine and passed spontaneously per anum. When no other symptom but colic is present, it is clear that a diagnosis of intestinal obstruction cannot be made.

The roentgenologist is the chief source of diagnostic aid. His evidence is derived from his observations of (1) the fistula, (2) the gallstone within the bowel and (3) the obstructed bowel independent of whether or not a gallstone can be visualized.

A scout film of the abdomen may confirm the clinical impression of an obstructed bowel and even suggest the location of the obstruction. As the stone moves along there may be a progressive shift in the localization of the gas within the bowel as revealed by roentgenograms. The majority of these gallstones are not visible in the roentgenograms, but occasionally the obstructing stone can be seen. Distended loops of bowel may obscure the stone. In 3 of my patients an opaque object was seen within the bowel but not identified as a stone. In 3 others a definite diagnosis of an obstructing gallstone was made by roentgen examination, helped in 1 case by the history of recent defecation of a gallstone. When a Miller-Abbott tube has been successfully passed into the small intestine, the introduction of a small amount of thin barium sulfate after the downward progress of the tube has been halted may delineate the impacted stone. In the majority of cases in which correct preoperative roentgen diagnosis of gallstone ileus has been made, the oral administration of barium sulfate has demonstrated the obstructing stone as a filling defect occluding the intestinal lumen. Such a practice is of course dangerous but is periodically resorted to in cases of gallstone ileus, because of the obscure course of the obstruction.

The diagnosis by roentgen examination of cholecystoenteric fistula is additional evidence pointing to the possibility of gallstone ileus, although such a fistula may be long standing and unrelated to the present obstruction. Borman and Rigler made a comprehensive study of fistulas of this type. They advised spot films over the region of the gallbladder in addition to the routine scout film of the abdomen. The biliary radicals may be outlined by the presence of gas within the ducts. This was the case in 2 patients in my group. However, a similar roentgen appearance can result from incompetency of the sphincter of the common duct due to the passage of a large gallstone or from duodenal ulceration in the vicinity of the lower end of the common duct. Roentgen examination may show absence of gallstones from a gallbladder in which their previous presence had been demonstrated. Cholecystograms show no filling of the gallbladder when such a fistula exists.

When barium sulfate is given by mouth in the presence of a cholecystoduodenal fistula, the fistula and biliary tree are usually outlined by the regurgitation of barium sulfate from the intestinal tract. Borman and Rigler emphasized characteristic changes in the mucous membrane

adjacent to the intestinal stoma of the fistula. These consist of irregular folds of mucous membrane with loss of elasticity. There may even be stenosis of the bowel at this point. Multiple fistulas to the bowel and nearby organs are not rare. At times an enema of barium sulfate reveals a cholecystocolic fistula, and there have been 2 cases at the Salem Hospital in which the stomach has been filled with barium sulfate given by rectum. The patient in case 1 was given an enema of barium sulfate on March 21, 1940. After the barium sulfate reached the hepatic flexure, it extravasated into the biliary ducts, the duodenum and the stomach. The sinus tract to the upper part of the gastrointestinal tract was in the region of the first and second portions of the duodenum (fig. 2).

#### TREATMENT

Hardly any type of intestinal obstruction challenges the surgeon's judgment more than gallstone ileus. In one sense newer methods of treatment complicate rather than simplify the therapeutic problem. Prior to the development of nonsurgical decompression, the clinical condition of the patient with intestinal obstruction was manifested by his symptoms of persistent pain, nausea and vomiting and by distention. These signs and symptoms are abolished by adequate suction decompression through an inlying tube. Gallstone ileus represents a simple mechanical obstruction without the threat to the blood supply of the bowel until late. Tenderness is not characteristic of the clinical picture. However, if operation is delayed too long, two catastrophes may ensue with little or no warning so long as medical decompression is carried out. The incarcerated stone may ulcerate through the wall of the bowel, or perforation of the bowel proximal to the stone may occur. The difficulty of complete evacuation of the small intestine may permit distention in several feet of bowel proximal to the site of the stone, and this amount of distention may escape both clinical and roentgenologic detection. The site of obstruction is usually low in the small bowel. In the last case of gallstone ileus at the Salem Hospital the fact of a persistent obstruction in the small intestine was not recognized until late, owing partly to the elimination of the evidence for obstruction by suction decompression. Multiple perforations occurred in the small intestine proximal to the stone even though clinical signs of obstruction were inconclusive in the presence of suction decompression.

In a recent study of 136 cases of acute mechanical obstruction of the small bowel at the Massachusetts General Hospital, McKittrick and Sarris<sup>18</sup> made the striking observation that not a single death occurred in a group of 43 patients operated on within twenty-four hours of the

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18. McKittrick, J. B., and Sarris, S. P.: Acute Mechanical Obstruction of Small Bowel: Its Diagnosis and Treatment. *New England J. Med.* 222:611, 1940.

onset of their obstruction. Operation should be performed in a case of gallstone ileus as soon as it is apparent that the progress of the stone has stopped and that more or less complete obstruction of the bowels exists.

When a patient is suffering cramps, perhaps in varying locations of the abdomen unaccompanied by vomiting and distention, observation may be carried out for a period during which rest in bed, use of antispasmodics and a liquid diet can be instituted while the abdomen is studied by repeated clinical and roentgen examinations. In my series such a situation due to a gallstone which later was passed per anum existed in 2 persons. Intestinal intubation may be desirable as an aid in the localization of the gallstone within the intestine by the use of thin barium sulfate introduced through a tube. Its employment in a case of actual obstruction in place of immediate operation and with the object of relieving a spastic obstruction is a dangerous practice in my opinion, although Wangenstein mentioned 2 patients with small stones and some degree of spastic obstruction who were treated with inlying suction decompression and then passed the gallstones in the stools. As an adjunct to immediate operation it is of course useful. When such decompression is practiced on a patient whose condition does not permit immediate operation, a surgical procedure should nevertheless be carried out at the earliest possible moment if the obstruction is persistent as demonstrated by clamping the tube or if in the meantime studies have revealed a stone within the lumen of the bowel.

Enterotomy is the operation of choice. Enterostomy is usually unnecessary, as adequate decompression of the bowel above the stone can be secured by the Miller-Abbott tube, which should be passed into the duodenum preoperatively. When possible, the obstructing stone should be milked upward a short distance so that the opening in the bowel is not made at the point of incarceration, where wound healing may be poor. The longitudinal incision should be closed transversely by an inverting type of suture and reenforced by a continuous Cushing stitch followed by a row of interrupted mattress sutures. It is unwise to attempt to crush the stone within the lumen of the bowel, because such an effort may result in dangerous trauma to the wall of the intestine. Adhesions and kinking of the bowel may be minimized by tacking a free omental graft over the suture line with a few interrupted sutures. The protection of the margins of the wound from contamination at the time of enterotomy is particularly important. The contents of the blocked intestine are extremely infectious, owing partly to the draining biliary fistula. It is desirable to employ some impermeable pad against the wound, such as the cellophane-lined pad

advocated by Lahey.<sup>19</sup> In this series wound sepsis occurred in 6 instances. In 2 women who recovered there was sloughing of the fascia. Three of the 6 patients died, and in 2 of them the extent of the wound sepsis appeared to play a significant role in causing their death.

The possibility of multiple gallstones must be kept in mind at operation. In 3 of Holz's<sup>20</sup> series of 5 cases of repeated operation for gallstone ileus, the second stone had to be removed during the immediate convalescence from the first operation. It is probable that the second stone was already in the intestine at the time of the first operation. Numerous authors have reported the presence of multiple stones in the intestine at operation, often close together but sometimes separated by considerable distance. The presence of facets on the obstructing stone indicates the need for additional search provided the patient's condition permits. The proximal parts of both the intestine and the biliary tract should be palpated. Detection of stones within the gallbladder may be difficult owing to dense adhesions. Additional stones can often be removed from the intestine through a single incision. However, it will rarely be feasible to perform any operation on the gallbladder after removing the stone from the bowel.

Reports of 9 cases of recurrent gallstone ileus have been published. One of the patients was operated on by me and was the oldest patient on record to recover from two bouts of obstruction both necessitating enterotomy.<sup>21</sup>

CASE 5.—E. D., a 79 year old woman, had known for seven years that she had what was thought to be a single gallstone within the gallbladder. She never had any biliary symptoms except mild indigestion. In March 1939 she had intestinal colic followed by the defecation of two gallstones. Shortly thereafter she had intestinal obstruction and an impacted gallstone was removed from the jejunum. The weight and the diameter of this stone were less than the weight and the diameter of one of the stones defecated a few weeks earlier, with which she had had colic only. Three months later a second jejunotomy was performed to remove another impacted stone (fig. 5).

The distinction between colic and ileus is nicely illustrated by the case just reported. Moreover the removal of one faceted stone makes it necessary to search for additional stones in the intestine or the gallbladder.

The management of the biliary fistula should be regarded as a separate problem. If studies demonstrate a fistula from the gallbladder

19. Lahey, F. H.: A Waterproof Laparotomy Pad of Gauze and Cellophane, *J. A. M. A.* **104**:1990 (June 1) 1935.

20. Holz, E.: Zur Frage des Gallensteinileus, *Arch. f. klin. Chir.* **155**:166, 1929.

21. Hinchey, P. R.: Recurrent Gallstone Ileus. *New England J. Med.* **223**:174, 1940.

to the stomach, the duodenum or the upper part of the jejunum, it seems justifiable to do nothing about the fistula unless symptoms of cholangitis develop. McQueeney<sup>22</sup> cited 2 instances of cholecystoduodenal biliary fistula of nineteen and fifteen years' duration respectively, without evidence of cholangitis. The majority of the patients are old, and closure of the fistulous communication with the bowel is considerably hazardous. Most authors are opposed to immediate attack on the biliary fistula. There have been cases in which cholecystectomy has been performed after a previous fistula from the gallbladder had closed spontaneously. In such cases dense adhesions are encountered.

However, if the gallbladder has drained into the colon, cholangitis is a common sequel and is characterized by chills, fever and loss of weight. Wakefield, Vickers and Walters expressed the opinion that it is unsafe to await the development of clinical cholangitis and hepatitis with any cholecystoenteric fistula. There were 32 cholecystocolic biliary fistulas in their series, and 19 of the patients had recently lost 15 to 40 pounds (6.8 to 18.1 Kg.). They recommended early operation on the fistulous tract irrespective of whether it drained into the small or the large intestine. Closure of a cholecystocolic fistula seems desirable if the patient's condition will permit.

#### SUMMARY

Thirteen cases of gallstone ileus are reviewed.

Gallstone ileus is a complication of chronic disease of the biliary tract. Its occurrence will be lessened by earlier operation on the biliary tract.

Salient points in diagnosis and treatment are discussed.

Dr. Howard M. Clute and the members of the Salem Hospital surgical staff gave permission to use their cases.

355 Essex Street.

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22. McQueeney, A. M.: Internal Biliary Fistulae and Intestinal Obstructions Due to Gallstones, *Ann. Surg.* **110**:50, 1939.

# PULMONARY EMBOLISM

## CLINICAL AND EXPERIMENTAL STUDY

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OAK PARK, ILL.

AND

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Any discussion of pulmonary embolism must concern itself primarily with a consideration of the fundamental problem of venous thrombosis. Many years ago Virchow,<sup>1</sup> Aschoff<sup>2</sup> and Welch<sup>3</sup> set forth the fundamentals of the mechanics of red and white thrombus formation, which can still be found in any modern textbook. Innumerable publications on pulmonary embolism and thrombophlebitis have since confirmed the findings of the original investigators.

The word thrombophlebitis poorly describes the spontaneous venous thrombosis which occurs postoperatively and in medical patients at rest in bed, because the ending of the word suggests that inflammation is present. Any inflammation in the wall of the vein or in the thrombus is a secondary manifestation and not a primary cause. The type of thrombophlebitis caused by local trauma or infection does not pertain to this discussion. Our concern is with spontaneous intravenous clotting, and this will be referred to in the paper by the more descriptive term phlebothrombosis, which was popularized by Ochsner.<sup>4</sup>

The causative factors in the production of phlebothrombosis are presumably many, and the importance of each has been reviewed.<sup>5</sup> It is rather generally accepted, however, that retardation of venous blood flow is the primary cause. If slowing of the venous circulation is responsible for thrombus formation, it should be possible to produce it

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Read before the Section on Surgery, General and Abdominal, at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 11, 1942.

1. Virchow, R.: Neuer Fall von tödlicher Embolie der Lungenarterien. *Arch. f. path. Anat.* **10**:225-228, 1856.

2. Aschoff, L.: Thrombosis, *Arch. Int. Med.* **12**:503-525 (Nov.) 1913.

3. Welch, W. H.: Thrombosis and Embolism, in Allbutt, T. C.: *System of Medicine*, New York, Macmillan & Co., 1898, vol. 6, pp. 155-285.

4. Ochsner, A., and De Bakey, M.: Thrombophlebitis and Phlebothrombosis: C. Jeff Miller Lecture, *South. Surgeon* **8**:269-290, 1939.

5. Potts, W. J.: Pulmonary Embolism, *Ann. Surg.* **111**:554-563, 1940.



experimentally without injury to the intima of the vein, without the use of foreign bodies in the lumen of the vein and without the application of a caustic about the vein.

#### EXPERIMENTAL OBSERVATIONS

In the first series of 14 experiments on dogs under anesthesia induced with soluble pentobarbital U. S. P. (pentobarbital sodium), a silk ligature was placed around the midportion of the external jugular vein or the femoral vein just below Poupart's ligament and drawn tight

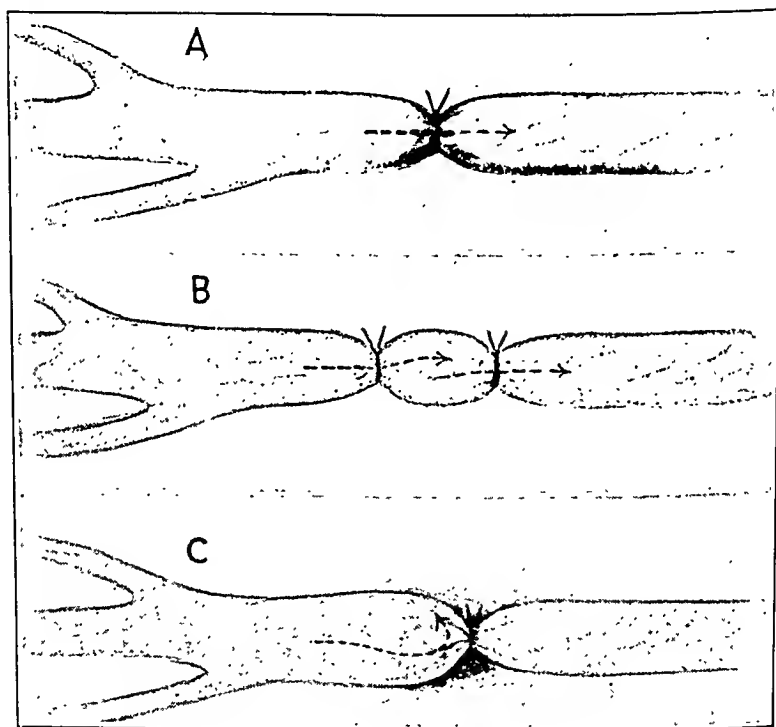


Fig. 1.—Forms of ligation used in the experimental production of thrombus formation. *A*, a silk ligature was placed around the midportion of the external jugular vein or the femoral vein just below Poupart's ligament and drawn tight enough to throttle the blood flow to one half or two thirds of normal. *B*, the external jugular and femoral veins were doubly partially throttled with silk ligatures placed 1 or 2 cm. apart. *C*, the external jugular and femoral veins were completely ligated with a single silk ligature.

enough to throttle the blood flow to one half or two thirds of normal. All animals were killed at the end of seven days. In no instance was there the slightest gross evidence of thrombus formation (fig. 1 *A* and table 1). The negative results suggested that the whirls and eddies of blood described by Aschoff as necessary for thrombus formation

had not been produced. In the Mississippi River in Minnesota, where the stream is wide and shallow and the current is slow and tortuous, there are innumerable islands and shoals. Farther downstream, where the river is deep and the current swift, sediment does not have a chance to accumulate and build up "thrombi."

In a second series of experiments the external jugular and the femoral vein were doubly partially throttled with silk ligatures placed 1 to 2 cm. apart (fig. 1 *B*). It was demonstrated at the close of the operation that blood would flow through the constricted portion of the vein. The only injury to the vein was that incidental to its exposure. All the animals were killed at the end of one week. All specimens were removed while the dog was alive but under anesthesia to avoid mistaking on gross examination a postmortem for an antemortem thrombus. The results are summarized in table 1.

With the exception of one thrombus the size of a grain of wheat, there were no thrombi in 14 external jugular veins one week after

TABLE 1.—*Data on the Experimental Study of Pulmonary Embolism*

Ligation	External Jugular Vein	Thrombosis	Femoral Vein	Thrombosis
Single partial.....	7	0	7	0
Double partial.....	14	1*	22	13
Single complete.....	7	1	12	3†

\* Thrombus was the size of a grain of wheat.

† One of these was a tiny thrombus.

double partial ligation. In the femoral veins, on the contrary, thrombi formed between the ligatures or caudal to the distal ligature or both in 13 to 22 veins one week after double partial ligation. In no instance was a thrombus found cephalad to the proximal ligature.

Why thrombosis should occur in the femoral vein and not in the external jugular vein when the procedure was exactly the same in each is a matter of conjecture. That there are valves in the femoral vein and not in the external jugular vein may be of importance. Of more significance probably is the fact that in the dependent legs the return flow of venous blood is retarded. The animal confined in a small cage has little opportunity to exercise but can move the head freely. Guesswork is not in order. The fact remains and is significant that thrombi were formed in several of the femoral veins subjected to double partial ligation but not in the external jugular veins similarly treated.

Grossly these thrombi were dark red masses with grayish white streaks and patches in and about them (fig. 2). The thrombi measured 1 to 5 cm. in length, the average being about 2 cm. In most but not all

instances the clot completely filled the lumen of the vein but was so loosely attached to the intima that unless great care was exercised during removal of the vein the clot fell out. At postmortem examination no emboli were found in the lungs. There was no instance of swelling of the hindleg in those animals in which the femoral vein was completely occluded by thrombus.

*Microscopic Examination (Dr. Carl W. Apfelbach).*—In the sections (labeled dog 41) of the femoral veins and contained thrombi stained with hematoxylin and eosin and with phosphotungstic acid and hematoxylin there were mixed thrombi. One half of each thrombus was partially canalized and contained remnants of platelet masses. In the other half was a red clot in which there were beginnings of organization. In sections taken at another site, approximately half of the thrombus was white and the other half red. It did not completely occlude the lumen

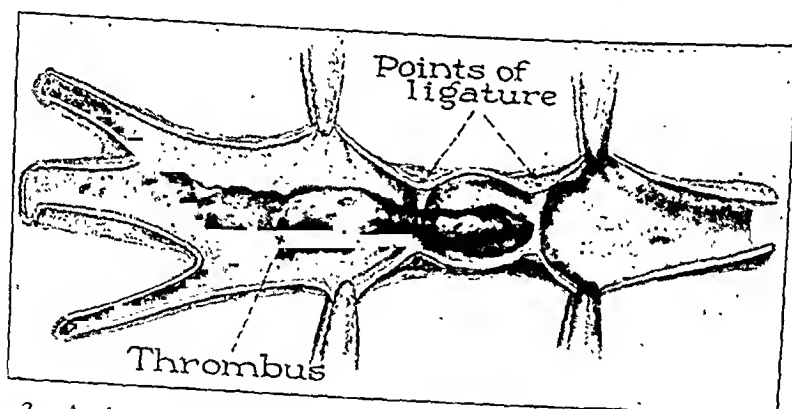


Fig. 2.—A thrombus which formed in a femoral vein one week after double partial ligation.

of the vein. In similarly stained sections (labeled dog 42) the vein was occluded by a thrombus in the center of which were masses of agglutinated platelets and a few polymorphonuclear cells. Sections of the same vein taken at a different level showed organization in the periphery, but the main portion of the clot consisted of unidentifiable granular material. Near the periphery there were masses of agglutinated platelets. In still another section the thrombus was laminated—there were layers of agglutinated platelets separated by layers of red thrombus (figs. 3 and 4).

A third series of experiments was done in which the external jugular and the femoral vein were completely ligated with a single silk ligature (fig. 1 C). The object of this simple procedure was to determine whether thrombosis would occur under such circumstances and to compare the character of the clot with that formed in a moving blood stream.

In 7 completely ligated external jugular veins there was 1 thrombus 2 cm. long distal to the ligature. In 12 completely ligated femoral veins 2 moderate-sized thrombi and 1 tiny thrombus appeared distal to the ligature. These thrombi were typical stagnation clots confirmed by microscopic examination (fig. 5).



Fig. 3.—Photomicrograph of a section of a thrombus formed in a femoral vein by double partial ligation.

#### CLINICAL CONSIDERATIONS

Inactivity, we believe, is one of the important causes contributing to retarded circulation and consequent thrombosis. When the muscles of the legs and the abdomen are inactive, there is retardation of blood

flow in the pelvic and femoral veins and their tributaries. Smith, Allen and Craig<sup>6</sup> showed that exercises of the legs decrease the circulation time from the foot to the carotid sinus; that elevation of an extremity decreases the circulation time in that extremity; that warmth of the



Fig. 4.—Photomicrograph of a section of a thrombus formed in a femoral vein by double partial ligation.

skin decreases the circulation time, and that coldness increases it. They stated that the venous blood flow is retarded after operation and con-

6. Smith, L. A.; Allen, E. V., and Craig, W. M.: Time Required for Blood Flow from the Arm and from the Foot of Man to the Carotid Sinus, *Arch. Surg.* **41**:1366-1376 (Dec.) 1940.

cluded that "This factor probably is important in the genesis of post-operative thrombosis and embolism."

Why is phlebothrombosis rare in the axillary veins if not because the rather constant action of the muscles and the frequent elevation

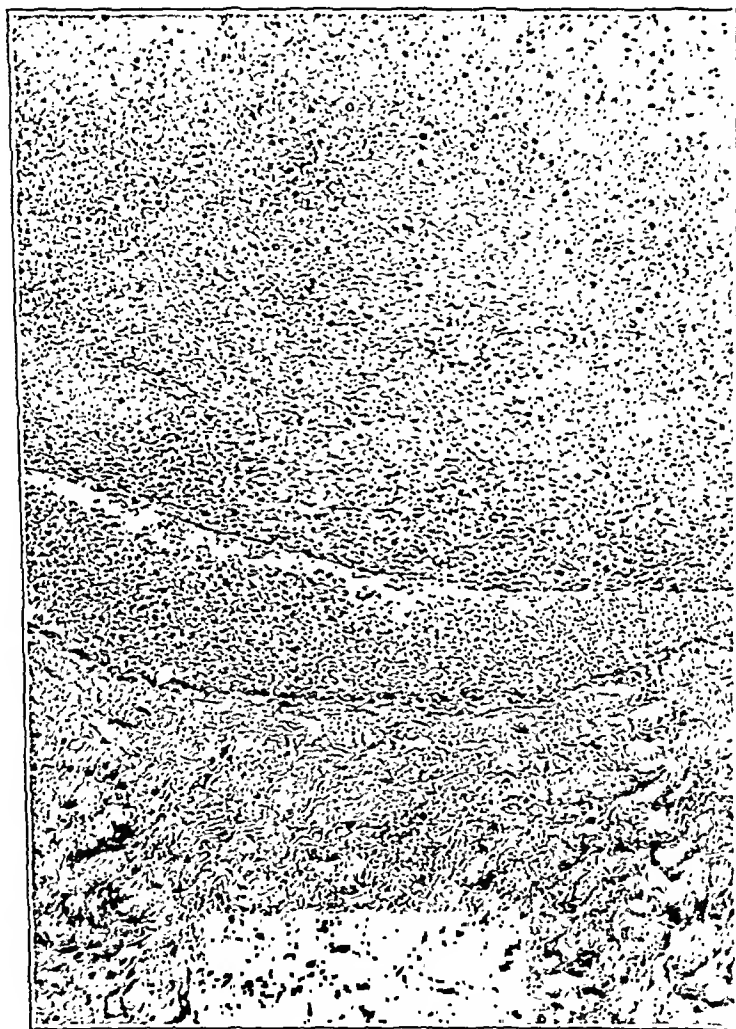


Fig. 5.—Photomicrograph of a section of a thrombus formed in an external jugular vein by complete ligation.

of the arms prevent the accumulation of clot-forming elements? Thrombosis is common in patients with fractures necessarily confined in restraining plaster encasements but rare in patients with fractures of equal severity which can be treated by ambulatory methods. The only varying factor is activity.

Cardiac weakness,<sup>7</sup> shallow respiration, forced inactivity, low blood pressure, abdominal distention, tight abdominal binders, pillows beneath the knees, pressure of one leg against the other, pressure of Poupart's ligament against the femoral vein—all of these in a measure combine to simulate the experimental condition of retarded circulation already described. When to these are added old age, obesity, cachexia, depression of the circulation by drugs, dehydration increasing the viscosity of the blood, varicosities in the legs, altered blood chemistry and physical depression, one wonders why phlebothrombosis and pulmonary embolism are such relatively rare postoperative complications.

During the past few decades most of the efforts toward the prevention of pulmonary embolism have been focused on the prevention of venous stasis in the legs. Krecke,<sup>8</sup> Pool,<sup>9</sup> Blair,<sup>10</sup> Gamble,<sup>11</sup> Barnes,<sup>12</sup> Ochsner and De Bakey<sup>13</sup> and others have advised postoperative breathing and leg exercises. Schmid,<sup>14</sup> DeCourcy,<sup>15</sup> Gray<sup>16</sup> and de Takats<sup>17</sup> advised elevation of the foot of the bed to aid the return of venous blood. Walters<sup>18</sup> increased the rate of blood flow by the administration of thyroid. In fact, there are few surgeons who do not appreciate the importance of as much activity as possible for all patients who are confined to bed.

7. Belt, T. H.: Thrombosis and Pulmonary Embolism, *Am. J. Path.* **10**:129, 1934.

8. Krecke, A.: Ueber Vor- und Nachbehandlung bei Bauchoperationen, insbesondere über das frühzeitige Aufstehenlassen, *München. med. Wchnschr.* **57**: 2037-2041, 1910.

9. Pool, E. H.: Systematic Exercises in Postoperative Treatment, *J. A. M. A.* **60**:1202-1204 (April 19) 1913.

10. Blair, B., in discussion on Glynn, E.: Pulmonary Embolism, *J. Obst. & Gynaec. Brit. Emp.* **31**:521, 1924.

11. Gamble, H. A.: The Prevention of Postoperative Embolism and Phlebitis, *Am. J. Surg.* **28**:93-95, 1935.

12. Barnes, A. R.: Pulmonary Embolism, *J. A. M. A.* **109**:1347-1352 (Oct. 23) 1937.

13. Ochsner, A., and De Bakey, M.: Therapy of Phlebothrombosis and Thrombophlebitis, *Arch. Surg.* **40**:208-231 (Feb.) 1940.

14. Schmid, H. H.: Verhütung von Thrombosen und Embolien, *Arch. f. Gynäk.* **161**:401-404, 1936.

15. DeCourcy, J. L.: Venous Stasis as Cause of Postoperative Embolism: Its Prevention by Use of Reverse Fowler Position After Lower Abdominal Operations, *Anesth. & Analg.* **8**:342-345, 1929.

16. Gray, H. K.: The Use of the Trendelenburg Position in the Prevention of Postoperative Pulmonary Complications, *Proc. Staff Meet., Mayo Clin.* **9**:453-454, 1934.

17. de Takats, G., and Jesser, J. H.: Pulmonary Embolism: Suggestions for Its Diagnosis, Prevention and Management, *J. A. M. A.* **114**:1415-1421 (April 13) 1940.

18. Walters, W.: Method of Reducing Incidence of Fatal Postoperative Pulmonary Embolism, *Surg., Gynec. & Obst.* **50**:154-159, 1930.

In a series of experiments<sup>19</sup> we demonstrated that simultaneous elevation of both hindlegs of a dog increased the rate of venous blood flow in the inferior vena cava from 100 to 250 per cent. Sweeping out of the veins the beginning of accumulations of formed elements of the blood should, if attainable, lessen the incidence of thrombosis.

Beginning in 1928, one of us (W. J. P.) decided to adopt routine breathing and leg exercises for all adult patients unless their condition was such that it seemed inadvisable. The following order is written and takes effect the evening of the operation or the morning after operation: "Have the patient take fifteen deep breaths each morning and evening and with each breath actively flex the legs." The choice of fifteen was purely arbitrary. So long as the patient goes through the night without active exercise there seemed no object in repeating them oftener than twice a day. If any scheme of postoperative activity is adopted, it must be followed through with instruction of the nursing

TABLE 2.—*Data on the Clinical Study of Pulmonary Embolism*

	Number	Phlebo- throm- bosis	Pulmonary Infarction	Fatal Pulmonary Embolism
Postoperative patients who did breathing and leg exercises .....	837	0	0	0
Patients with fractures requiring immobilization of one or both legs.....	124	5	6	0
Postoperative patients who did no exercises..	150	4	1	1

and the resident staff. Occasional meetings with the nursing and the resident staff to explain the object of this regimen is beneficial in securing cooperation. Too often the type and the amount of postoperative activity are left to the discretion of the nurse, who follows the indefinite verbal order of the surgeon to keep the patient active.

Before giving personal statistics (inconclusive because the number is small), it is fitting to quote from a previous publication: "Coincidence often leads us astray in the evaluation of therapeutic procedures." However, during the past thirteen years there has been no occurrence of phlebothrombosis or pulmonary embolism among 837 private patients who carried out the routine postoperative breathing and leg exercises. During this same period the controls consisted of two groups: (1) 124 patients with fractures which required immobilization of one or both of the extremities and (2) approximately 150 patients who after a major operation did not or were not asked to carry out the postoperative exercises (table 2). In the first control group there were 5 cases of

19. Potts, W. J., and Smith, S.: Pulmonary Embolism: An Experimental Study of Variations in the Volume Blood Flow in the Inferior Vena Cava of the Dog, *Arch. Surg.* 42:661-664 (April) 1941.



phlebothrombosis, 4 of which were followed by pulmonary infarction, and 1 case of pulmonary embolism found at postmortem examination in a man who died five days after fracture-dislocation of the first lumbar vertebra complicated by transection of the cord. The origin of the emboli in this patient could not be found.

The clinical history of 1 patient not included in the group of control patients with fractures is of interest and if correctly interpreted supports the premise that inactivity is a causative factor in the production of thrombosis.

#### REPORT OF A CASE

Mr. V., a man aged 65, with moderately advanced Paget's disease of the right humerus, suffered a simple transverse fracture of this bone at the junction of the lower and the middle third. With the region under local anesthesia and with the aid of a fluoroscope, the fragments were replaced and fixed with molded plaster splints. The entire arm was firmly bound to the patient's chest with gauze bandage. He remained in the hospital three days but was ambulatory. Fourteen days after the fracture the patient complained of pain in the chest and spat up bright red blood. Because of the fixation apparatus adequate examination of the chest was impossible. Three days later there was recurrence of these symptoms. Both episodes were associated with fever. No sign of thrombophlebitis in the legs could be found. Dr. Robert Hemphill, the medical consultant, made a diagnosis of pulmonary infarction. Spontaneous recovery followed. The fixation apparatus was removed forty days after the fracture, when roentgenograms showed that satisfactory healing had occurred. The arm was swollen but not abnormally so, and no thrombosed veins could be palpated. In the absence of signs of thrombosis elsewhere, it seems fair to assume that the emboli originated in the veins of the immobilized arm.

In the surgical control group were 4 patients with phlebothrombosis. In 2 patients, women aged 49 and 58 respectively, thrombosis followed drainage of an appendical abscess. The woman who was 58 died instantaneously of pulmonary embolism. In a man aged 36 the phlebothrombosis followed release of mechanical intestinal obstruction, and in a woman aged 79 it followed abdominoperineal resection of the rectum. Following cholecystectomy in a woman aged 40 there was pulmonary infarction but no sign of phlebothrombosis.

To remind the nurses constantly that their patients must do the breathing and leg exercises and to demonstrate frequently to both patients and nurses how these are to be done is laborious. As a matter of fact, in the summer of 1935 they were discontinued for a time when doubts concerning their value arose. Promptly, extensive phlebothrombosis developed in a patient, and he died of pulmonary embolism (referred to already). This catastrophe, a coincidence most likely, nevertheless stimulated immediate reintroduction of routine breathing and leg exercises which have been continued since. That they are of some value there is little question. A negative virtue lies in the fact that they do

no harm. Certainly the patient who has been active in bed following an operation feels better on getting up than the patient who has been inactive.

#### SUMMARY

Experimentally we have demonstrated that thrombosis will occur in the femoral vein of a dog after double partial ligation.

Clinically it appears that a definite routine of postoperative breathing and leg exercises is of some value in lessening the incidence of phlebothrombosis and pulmonary embolism.

715 Lake Street.

#### ABSTRACT OF DISCUSSION

DR. GÉZA DE TAKÁTS, Chicago: The paper emphasizes the great importance of venous stasis in the formation of thrombi and consecutive emboli. Retardation of venous return has been demonstrated repeatedly on patients after operation or immobilization. Drs. Potts and Smith have clearly shown the factors which contribute to the slowing of circulation in bedridden patients. The interference with venous return is especially marked in the frequently employed Fowler position, during which stasis is produced in the pelvis, in the groin, and in the deep and muscle veins of the calves. To overcome this, the postoperative Trendelenburg position, maintained from twenty-four to forty-eight hours, is truly a great improvement and can be used for patients who are unable to carry out simple exercises.

Dr. Lawrence Petersen has recently tabulated the mortality following major amputations at the Research and Educational Hospitals. There were 110 major amputations between 1927 and 1942, and 9 patients died, giving a mortality of 8 per cent. Only 1 patient died of embolism, and this was a person with polycythaemia vera who had been treated with leeches up to the fifth day and died on the sixth, after the use of leeches was discontinued. Only 1 patient in this group had a ligation of the femoral vein. In the experience of my associates and me, then, pulmonary embolism does not occur frequently after amputations, the incidence being not more than 1 or 2 per cent.

Recently we have attempted to study the clotting mechanism of patients by determining their response to heparin. Roughly, all individuals fall into one of three groups. Their response to heparin is normal, exaggerated, or diminished.

In spite of the great importance of venous stasis, one should not forget that coagulation of blood is favored in the postoperative state. Heparin or other anticoagulants obviously cannot be given to all postoperative patients, but the endangered group may be picked out by their response to heparin. For such patients all available measures against thrombosis must be carried out with the greatest vigor.

DR. EDGAR V. ALLEN, Rochester, Minn.: Theoretically there are three possible mechanisms for postoperative venous thrombosis. One of these is an increased tendency of the blood to clot. However, in spite of assiduous studies, no one has shown conclusively that there exists such an increased tendency after operation. There are some conditions of the blood which predispose to venous thrombosis following operation, but in the vast majority of patients who are operated on there are no significant changes in the coagulation of the blood after operation.

A second factor is the possibility of trauma to veins. I am told that assistants do not lean on a femoral vein during a major operation and that usually no other trauma occurs. Yet it is known that after such operations as cholecystectomy thrombosis of the femoral vein may occur. For those who advocate the theory of trauma, there is some evidence in support as shown by the fact that the incidence of postoperative venous thrombosis following pelvic operations is three times as great as the incidence following operations on the upper part of the abdomen. There is no evidence that this trauma to veins is a significant, persistent cause of postoperative venous thrombosis.

The third possibility, one which is the subject of the discussion today, is the question of slowed circulation of venous blood. As Dr. Potts has indicated, Smith and I have made studies of circulation time and have shown that after an operation there is a fairly constant reduction in the speed with which the blood flows through the veins of the lower extremities. This begins on the second or third postoperative day; the blood flows progressively more slowly through the veins of the lower extremities, until the patient becomes ambulatory.

How does this fit in with what is known about postoperative venous thrombosis? Similar studies on the circulation of blood in the veins of the upper extremities indicate that there is no significant slowing of the speed of circulation in the upper extremities. That might explain why postoperative venous thrombosis occurs so frequently in the lower extremities and so infrequently in the upper extremities. The fact that the maximum slowing of the venous circulation is on about the eighth to the twelfth postoperative day would fit in well with the observation that that is the period at which postoperative venous thrombosis occurs in the vast majority of instances. This slowed circulation of the blood in the veins would explain also why the administration of thyroid sharply decreases the incidence of postoperative venous thrombosis, and it would explain an observation which we have made that in approximately 1,200 operations (sympathectomy) for hypertension performed by neurosurgeons there has not been a single instance of postoperative venous thrombosis. Sympathectomy greatly increases the speed of flow of blood through the arteries and through the veins.

The evidence suggests that a slowed venous circulation is responsible for postoperative venous thrombosis, and Drs. Potts and Smith have added to the increasing evidence that this is true. Their evidence would be more conclusive were it not for the fact that the same procedure which produced venous thrombosis in the femoral vein failed to produce venous thrombosis in the jugular vein.

A word of caution about the interpretation of statistics. Postoperative venous thrombosis is known to occur only infrequently, and it is possible that in a large series of patients for whom nothing was done there might be no postoperative venous thrombosis merely because it does occur infrequently.

DR. LYMAN W. CROSSMAN, New York: My associates and I in my service at the City Hospital have approached the matter of postoperative embolism in what might be considered a physiologic way. We try to prevent the formation of postoperative emboli. Dr. de Takáts discussed retarding circulation and increasing circulation. What we do is stop circulation by Frederick M. Allen's method of applying a tourniquet to the extremity 6 or 8 inches (15 to 20 cm.) proximal to the line of cutaneous incision, refrigerating the entire extremity with ice, and after two and a half hours perform an amputation with no other anesthesia. At the time of the operation we always find that the blood is fluid. We never see a blood clot.

When the stump end is about ready to be closed and the tourniquet is taken off, the blood we see is always in a liquid form. The examination of the

blood drained from the specimen as it is removed has been examined and reported as being normal. Every one of the legs so treated has been examined under the microscope by Dr. James Lisa, our pathologist, and he has found no structural change as a result of the long refrigeration or the stasis and pressure brought about by the tourniquet. The tourniquet cuts off all circulation of blood and lymph and all nerve impulses. As most tourniquets are put on there is still an arterial trickle, which allows a flow of warm blood into a refrigerated extremity, and our precautions against this may explain why our patients have never had frost bite.

Dr. Allen has always emphasized the inhibition of thrombosis by cold, and, as we stated in the *ARCHIVES OF SURGERY* in January 1942, our group has encountered no instance of thrombosis or embolism with this method. As our series now comprises over 100 amputations, this experience appears significant.

DR. J. ROSS VEAL, Washington, D. C.: I have been interested in the freezing of the extremities. Dr. Crossman says it is a physiologic action. Speaking of physiology of circulation after freezing, if he cuts off arterial and venous circulation he creates an ideal situation in which thrombosis should occur provided it lasts long enough. Undoubtedly one can amputate an extremity after it is frozen, or partially frozen, without pain and the patient may return to the ward and be comfortable and carry on his diet, but I do not think freezing in any way prevents thrombosis. I think it creates a field in which thrombosis might develop if it persisted long enough.

There is one remark I should like to make about high ligation. It is known that clots from other parts of the body may lodge in the lungs. There have been cases in which the embolism came from the heart or some other vein of the body than that of the femoral stump, but I feel that the majority of the pulmonary complications following thigh amputations are embolic and that the emboli arise from the stump of the femoral vein.

DR. W. J. POTTS, Oak Park, Ill.: There is a great deal of mystery about pulmonary embolism. The causes are not known.

An interesting observation was made by a man in England, published in the *Lancet* some time ago. He showed that in a large city hospital, where casualties of various kinds from London came in the number of cases of pulmonary embolism in a group of a certain size under ordinary conditions was 6, but that during air raids the number of cases of pulmonary embolism in the same number of patients increased to 24. In other words, there was a 400 per cent increase in pulmonary embolism. He concluded that the reason for this was that the people sat in chairs in the air raid shelters, with the legs dependent, which caused thrombosis. I feel certain that the mechanical factor is the large one. If one could find how the clotting mechanism varies in patients it would be helpful.

Dr. Allen many years ago made, and a few years ago I repeated, a study on the relation of platelet count and coagulation time in postoperative patients and found that the latter varied from two to ten minutes, and yet there were no cases of thrombosis. As Dr. Allen so well pointed out, the whole thing may be a matter of coincidence, which, I wish to repeat, often leads physicians astray in the evaluation of procedures.

# WOUND HEALING

## EFFECT OF A STERILE ABSCESS ON FIBROPLASIA IN WOUND HEALING

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AND  
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PHILADELPHIA

The intermediary stages of the metabolism of endogenous protein have been the subject of considerable interest from the time of the earliest studies on the physiology and biochemistry of nutrition. Recently interest has been renewed or accentuated because of the increasing recognition of the importance of hypoproteinemic states in clinical medicine. The recent attempts by Elman, Farr and others<sup>1</sup> to build up tissue and plasma protein by supplying protein precursors intravenously emphasized the need for greater knowledge concerning the utilization of these materials by the organism.

One of the least understood phases in this endogenous cycle is the fate of the protein-split products released by catabolism of tissue protein. It is important to know whether these products are available, wholly or in part, for the repair of damaged tissues and for the replenishment of protein stores in the liver and the circulating plasma.

Madden and Whipple and co-workers<sup>2</sup> found that the presence of a sterile abscess induced by the injection of turpentine markedly delayed the regeneration of plasma protein in dogs consuming an ample diet. They felt that the sharp reduction in the curve of regeneration during the first twenty-four hours reflected in part the extravasation of plasma protein into the damaged tissues. However, they maintained that a true disturbance of the mechanism for producing plasma protein also occurred.

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From the Harrison Department of Surgical Research, University of Pennsylvania, School of Medicine.

1. Elman, R., and Weiner, D. O.: *Intravenous Alimentation, with Special Reference to Protein (Amino Acid) Metabolism*, J. A. M. A. **112**:796 (March 4) 1939. Elman, R.: *Proc. Soc. Exper. Biol. & Med.* **36**:867, 1937. Farr, L. E., and McFayden, D. A.: *ibid.* **42**:445, 1939.

2. Madden, S. C.; Winslow, P. M.; Howland, J. W., and Whipple, C. H.: *J. Exper. Med.* **65**:431, 1937.

Ravdin, Goldschmidt and Vars<sup>3</sup> showed that diets rich in protein protected the livers of rats from damage by anesthesia induced with chloroform. They expressed the opinion that protein or some fraction of protein leads to a reduction of the amount of preexisting liver lipid which predisposes to hepatic injury by chloroform and that adequate reserves of protein would lead to more rapid regeneration following injury. They showed also that the intramuscular administration of sodium ricinoleate protects rats receiving diets deficient in protein against hepatic damage. They expressed the belief that the protein-split products liberated locally and generally by the sterile abscess are utilized by the livers of these animals to maintain or replenish their protein stores.

In the experiments to be described in this paper an attempt has been made to determine whether or not the products of protein catabolism initiated by such a process are used by the organisms for tissue repair.

*Composition of the Diet Given to the Rats Used in the Experiments*

	Percentage
Sucrose.....	55.1
Dextrin.....	15.2
Lard.....	15.0
Butter.....	6.5
Bone ash.....	2.4
Salt mixture (Osborne and Mendel).....	1.2
Cod liver oil.....	2.0
Vegex *.....	5.0

\* Vegex is an autolyzed yeast extract.

#### METHOD

The curve of velocity of fibroplasia in the healing wounds of rats was chosen as the index of tissue repair. Adult albino rats weighing between 200 and 350 Gm. were selected. The animals were maintained throughout the experimental period on a diet containing approximately 1 per cent protein; the composition of the diet is given in the table. This was done in the hope that the effect of additional protein-split products made available by sterile abscess would be more evident.

The animals were given this diet for from ten to thirteen days preoperatively. Careful records of the food eaten and the weight lost by each animal were made during this period. The animals were then subjected to simple laparotomy. The anesthetic employed was sodium amytal (0.0005 mg. per gram of body weight) given intraperitoneally. Under aseptic precautions a midline incision was made through the skin, the muscles and the peritoneum of the anterior abdominal wall. The peritoneum and the muscles were closed as a single layer by a continuous stitch of no. 000 plain catgut. The skin was closed as a separate layer, a similar suture being used. After operation the animals were again given their preoperative diets, and records of the food eaten and the weight lost were kept as before. Half the animals received 0.08 cc. of a 10 per cent solution of sodium ricinoleate

3. Goldschmidt, S.; Vars, H. M., and Ravdin, I. S.: J. Clin. Investigation 18:277, 1939.

intramuscularly on the day of operation and on the third and sixth postoperative days. A different site for each injection was employed, the muscles of the neck and the shoulders and the upper portions of the lower extremities being chosen in succession.

Four to 6 rats from each of the two groups were killed daily, and the tensile strength of their wounds was determined. The method and the apparatus used in making these determinations were the same as those employed by Meade<sup>4</sup> in his studies on the tensile strength of the diaphragm. All animals showing infection in the wounds or at the site of injection were discarded.

### RESULTS

Practically all the rats lost weight steadily while taking the diet low in protein but remained in good condition otherwise. There were no significant differences in weight loss or food intake between the two groups (chart 1).

The catgut skin sutures disappeared at approximately the same time (three to five days) in the two groups. Residual segments of the deep catgut sutures persisted for six to ten days in all the animals of both groups, but the suture had consistently lost its continuity by approximately the sixth day. In general, integrity of the deep sutures was maintained longer in the rats given sodium ricinoleate.

Comparatively few wound infections occurred. Those that were observed had a catgut knot for their focus. Sodium ricinoleate consistently produced a sterile abscess at the site of injection. In some instances the abscess contained a small amount of glairy translucent amber fluid. No suppuration was encountered. The abscess wall was composed of inflammatory tissue containing many fibroblasts and leukocytes. There was considerable edema of the tissues surrounding the abscess. When the sodium ricinoleate had been placed too superficially, necrosis and gangrene of the skin resulted. In 5 cases sloughing of the gangrenous skin occurred.

Spontaneous evisceration was frequent during the first five days but showed no significant difference in group incidence. Evisceration during handling and injection occurred in approximately 1 of 6 animals in the group given sodium ricinoleate. These animals were immediately killed.

There was a rather high late mortality rate during the first eight days postoperatively, in both the control animals and those given sodium ricinoleate. Examination of those animals in which evisceration was not the cause of death usually failed to show any obvious gross pathologic changes. The mortality rate was approximately the same in both groups.

The variations between the individual determinations of tensile strength were too great to permit proper statistical treatment of the figures obtained. However, the general trend of the velocity of fibro-

4. Meade, R. H.: *J. Thoracic Surg.* 5:503, 1933.

plasia was obtained by plotting a curve of the average values of each group (chart 2). From the curves thus obtained a definite retardation of the velocity of fibroplasia can be seen in the group given sodium ricinoleate. The lag in fibroplasia is seen to be maximal during the

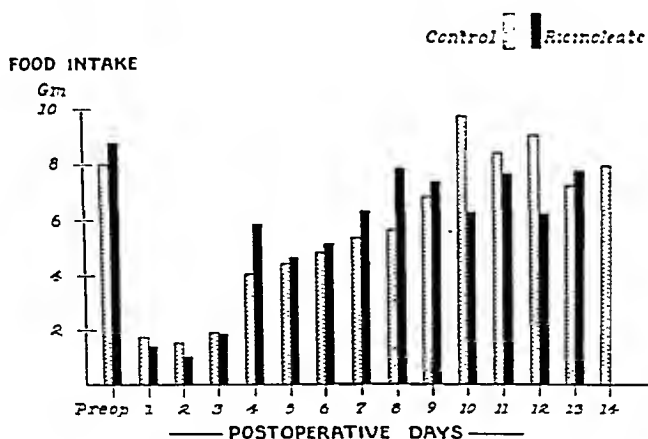


Chart 1.—Dietary intake of control rats and of those given sodium ricinoleate.

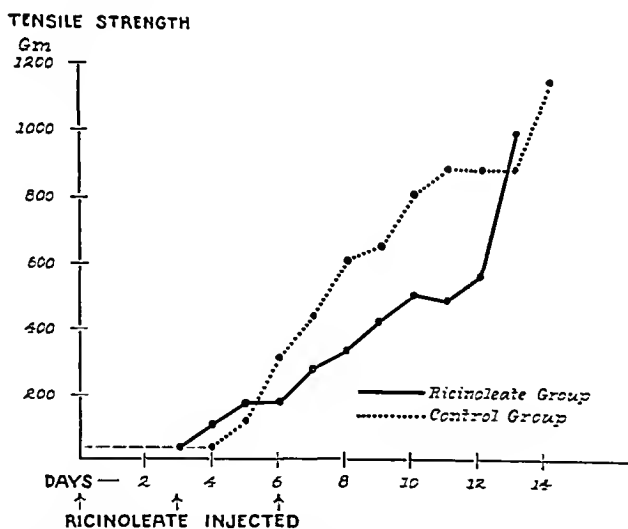


Chart 2.—Curve of velocity of fibroplasia in healing wounds of rats given a diet low in protein.

period from five to ten days after operation. The relation of the lag in fibroplasia to the period of injection of sodium ricinoleate should be noted. It also is of interest that fibroplasia began twenty-four hours earlier in the group given sodium ricinoleate than in the control group. The individual variations in tensile strength in the control group and the group given sodium ricinoleate are shown in charts 3 and 4.



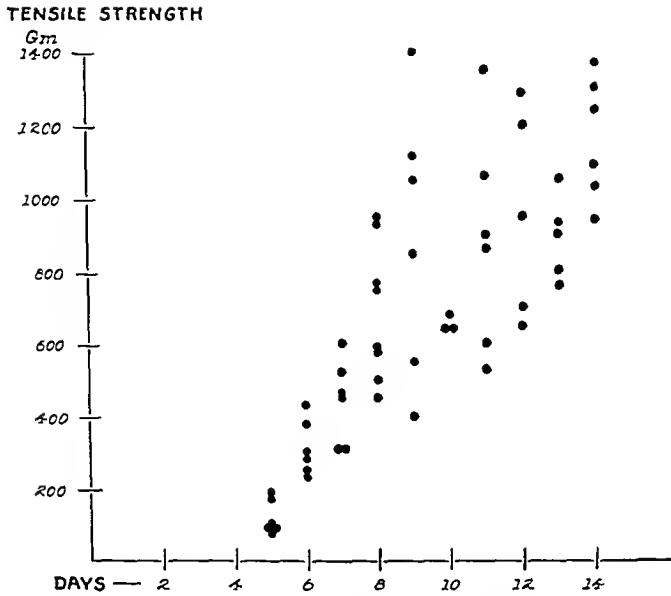


Chart 3.—Determinations of the tensile strength of wounds of rats in the control group.

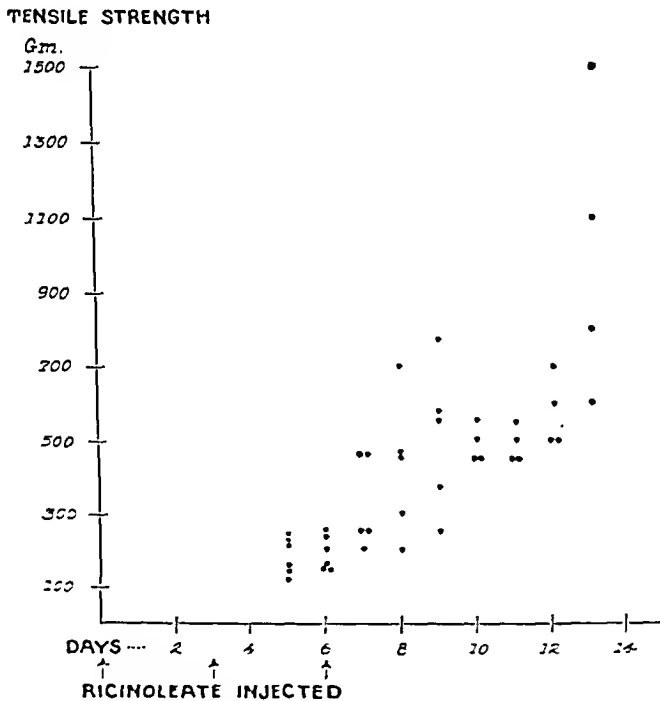


Chart 4.—Determinations of the tensile strength of healing wounds of rats given sodium ricinoleate.

## COMMENT

Studying the rate of cicatrization of wounds in dogs, Clark<sup>5</sup> reported that the feeding of diets high in protein abolished the latent period of cicatrization so that fibroplasia began immediately. With an adequate mixed diet the latent period was four days. A diet high in fat and low in protein increased the latent period to six days.

The careful experiments of Harvey and Howes<sup>6</sup> showed that feeding diets high in protein increases the velocity of fibroplasia in the healing stomach wounds of rats. The latent period was not affected in their experiments. They reported also that partial or complete starvation of adult rats at first caused a definite lag in fibroplasia during the first ten days but that a compensatory acceleration occurred during the last phase of the healing process which more than compensated for the initial lag. It is important in the light of the present experiments to emphasize that increased endogenous catabolism of protein in the starved and semistarved animals was stated by Harvey and Howes to be responsible for this acceleration.

In the present experiments it was hoped that a greater lag in fibroplasia would be produced by feeding a diet low in protein and that consequently the accelerating effect, if any, of endogenous protein catabolism would be magnified. In the experiments of Harvey and Howes<sup>7</sup> the increase in endogenous tissue breakdown was the result of starvation and appeared during the last phase of the healing process. In the present experiments, breakdown of tissue has been greatly increased by the injection of sodium ricinoleate and has been marked within twenty-four hours after the first injection or, in other words, by the end of the first postoperative day.

Comparison of the curves of velocity of fibroplasia in the two groups suggests that the injection of sodium ricinoleate retarded rather than accelerated fibroplasia. The general similarity of the two curves should be noted. The lag in fibroplasia in the animals given sodium ricinoleate occurs entirely in the first portion of the curve before it reaches a horizontal phase at the tenth day. In both curves there is a sharp increase in the velocity of fibroplasia after the twelfth and thirteenth days, respectively. It is interesting to observe that, in point of phase,

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5. Clark, A.: *Bull. Johns Hopkins Hosp.* **30**:117, 1919.

6. Harvey, S. C.: *Velocity of Growth of Fibroblasts in Healing Wound*, *Arch. Surg.* **18**:1226 (April) 1929. Harvey, S. C., and Howes, E. L.: *Ann. Surg.* **91**:641, 1930. Howes, E. L.; Briggs, H.; Shea, R., and Harvey, S. C.: *Effect of Complete and Partial Starvation Rate of Fibroplasia in Healing Wound*, *Arch. Surg.* **23**:846 (Nov.) 1933.

7. Howes, E. L.; Harvey, S. C., and Hewitt, C.: *Rate of Fibroplasia and Differentiation in Healing of Cutaneous Wounds in Different Species of Animals*, *Arch. Surg.* **38**:934 (May) 1939.

the curve of the group given sodium ricinoleate consistently precedes that of the controls by twenty-four hours. Thus, fibroplasia begins on the third day in the group given sodium ricinoleate and on the fourth day in the controls. The horizontal phase in the curve is reached by the tenth day in the animals given sodium ricinoleate, and not until the eleventh day in the controls. The secondary, compensatory rise in

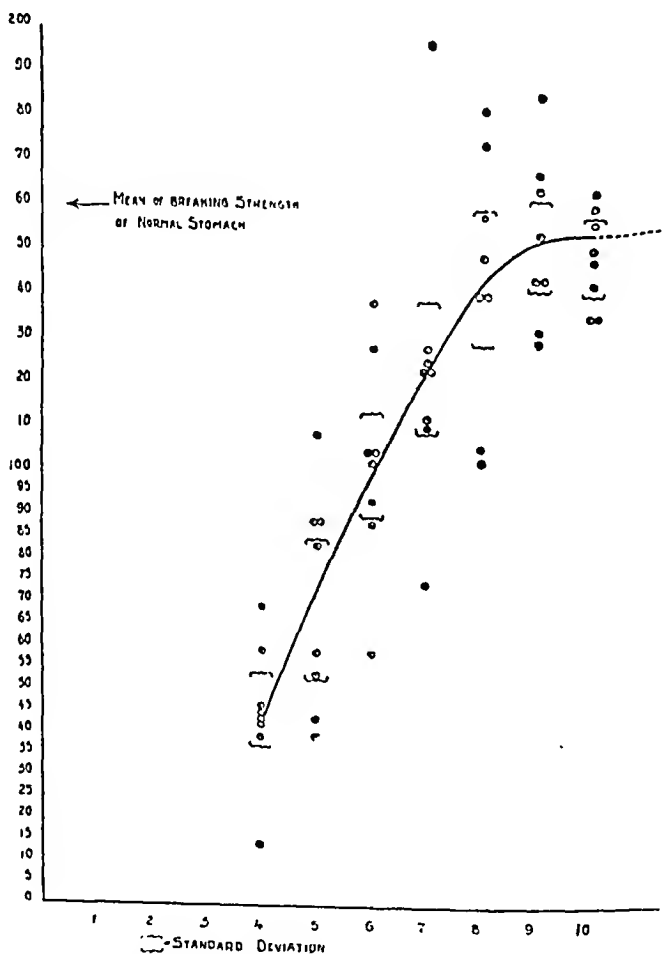


Chart 5.—Curve of velocity of growth of fibroblasts in healing wound of the stomach of the rat (after Harvey).

fibroplasia begins at twelve days in the group given sodium ricinoleate and at thirteen days in the control group, reaching average values of 1,000 and 1,160 Gm., respectively. The average tensile strength of the intact abdominal wall of rats fed for twenty-five days with the diet low in protein has been determined by the present methods to be 2,300 Gm. In Harvey's calculations the tensile strength developed in the healing wounds of the rat's stomach approximated that of the intact stomach by the tenth day (chart 5). Similar experiments on the tensile

strength of cutaneous wounds in the rat revealed that the incised wounds did not develop tensile strength equal to that of the intact skin until well past twenty days (chart 6).<sup>7</sup>

The criticism may be made that determinations of the tensile strength of a layered wound, such as an incised wound of the abdominal wall, cannot be expected to give uniformly significant results. Actually, however, only the strength of the musculofascial union, which functioned as a single layer, was tested in these studies. The cutaneous wound

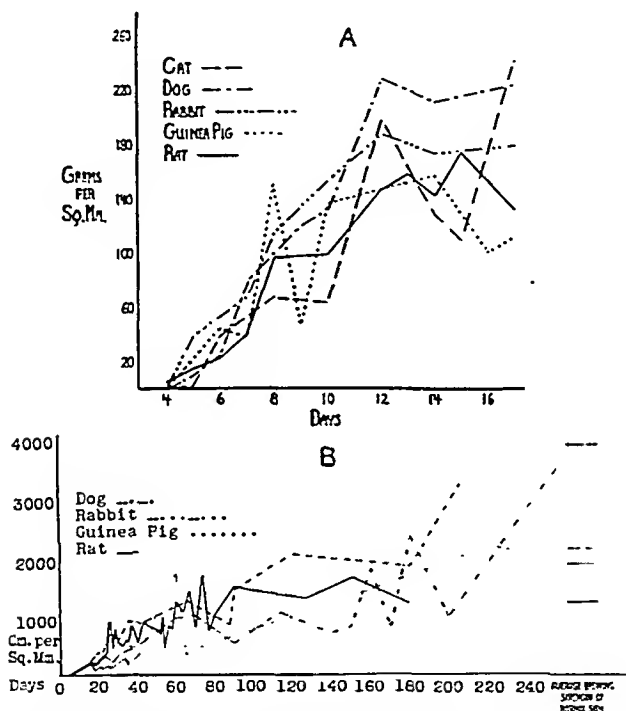


Chart 6.—*A*, early breaking strength of cutaneous wounds; *B*, later breaking strength of cutaneous wounds (after Howes, Harvey and Hewitt).

invariably gave way before the main wound, usually at a tension 200 to 300 Gm. less than the final calculation of tensile strength.

It is to be regretted that the curves of fibroplasia were not followed for at least ten to fifteen days more. Ravdin, Vars and Goldschmidt<sup>8</sup> demonstrated storage and utilization by the liver of the protein-split products liberated from sterile abscesses in the rat. There may well be an intermediate hepatic phase in the endogenous catabolism of tissue protein, which must take place before these products of protein degeneration can be utilized by the organism for tissue repair.

<sup>8</sup> S. Ravdin, I. S.; Vars, H. M., and Goldschmidt, S.: *J. Clin. Investigation* 18:633, 1939.

## CONCLUSIONS

The presence of a sterile abscess retards the velocity of fibroplasia in the healing wounds of rats on a diet low in protein.

This effect is most noticeable during the period from the fifth to the tenth day after operation.

No evidence is furnished by the results of these experiments that protein-split products liberated by the breakdown of tissue in the formation of a sterile abscess are utilized in wound healing.

A hepatic phase in the cycle of endogenous protein catabolism may be necessary before such protein-split products can be utilized by the organisms to repair damaged tissue.

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# FATE OF PROCAINE IN THE HUMAN BODY AFTER SUBARACHNOID INJECTION

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The great increase in the use of spinal anesthesia during the past two decades has been accompanied by a corresponding increase in the number of studies relating to its clinical aspects. But the basic question of the dynamics and fate of the drug itself has not been adequately treated. We therefore embarked on a program designed to develop and utilize trustworthy technics which would enable us to trace the course of the drug, determine what changes, if any, it underwent and find the site and the mechanism of these changes. While this program has not been completely fulfilled, we believe sufficient information has been gained to assist materially in the understanding of spinal and local anesthesia induced by procaine hydrochloride.

The first step was the development of a delicate analytic method for the determination of procaine in the various body fluids. Since it soon appeared that the procaine is rapidly detoxified, it was necessary to develop several supplementary procedures to enable us to distinguish each of the products of detoxication separately.

The basic reaction on which all the determinations reported here were based is the classic diazotization followed by coupling with an aromatic amine. The resultant dye is determined colorimetrically. When the determination is carried out thus on a native body fluid, the fraction is merely designated "free" and does not necessarily correspond to any single chemical entity. To determine procaine one makes the fluid alkaline with sodium carbonate and extracts it with ether. The ether solution is extracted with acid, and the diazotization reaction is carried out on the acid solution.

The alkaline solution remaining after the ether extraction may be acidified and diazotized in the usual way. The value thus obtained is the best measure of the amount of procaine which has been hydrolyzed.

"Total" designates the sum of the free aromatic amines and the acetylated or otherwise blocked amines which are hydrolyzed by boiling

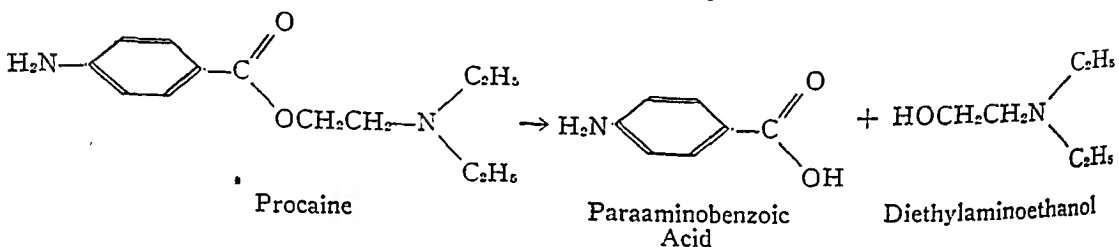
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From the Richard Morton Koster Research Laboratory.

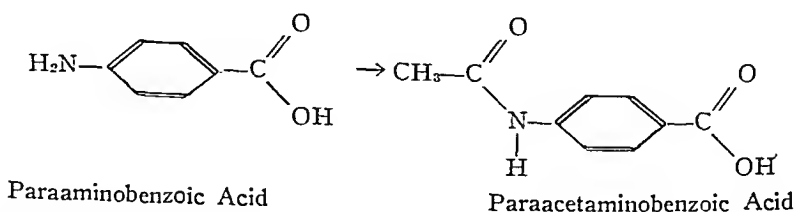
with hydrochloric acid. All values are expressed in terms of procaine equivalent.

When it is desired to determine a small amount of acetylated product in the presence of a much larger concentration of "free" substance, the following procedure is used: The diazotization is carried out as usual, but instead of proceeding with the coupling one heats the solution to destroy the diazonium salt and at the same time hydrolyze the acetylated portion. Then a second diazotization is carried out, followed by the usual coupling and the colorimetric determination. The details of these procedures will be reported in a subsequent communication.

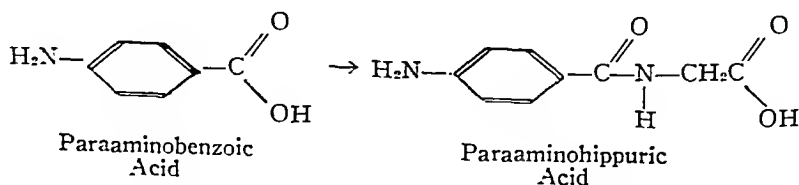
Before we present our results it may be desirable to summarize some of the possible biochemical reactions of procaine. Procaine may be hydrolyzed at the ester link to yield paraaminobenzoic acid and diethylaminoethanol. This reaction takes place slowly in pure water, but it may be accelerated by acid, alkali or other catalysts.



The products, paraaminobenzoic acid and diethylaminoethanol, are pharmacologically inert. Diethylaminoethanol can conceivably enter into a number of different reactions, but since distinctive analytic tests for it are lacking, its behavior in the body is at present unknown. It may well be excreted unchanged. On the other hand, paraaminobenzoic acid possesses functional groups the behavior of which in the body has been thoroughly studied. Like other aromatic amines, it may condense with acetic acid.



In analogy with the well known reaction of benzoic acid, the carboxyl group may condense with aminoacetic acid, yielding paraaminohippuric acid.



It is also known that a small percentage of ingested benzoic acid is excreted as the glucuronate. The same reaction may be expected in the case of the paraamino derivative. It is also conceivable that a hydroxyl group may be introduced into the nucleus, subsequently conjugating with glycuronic acid in a glucosidic linkage.

The fall in concentration of procaine following intrathecal injection has been the subject of several papers. It has been shown that at the site of injection there is a rapid initial fall in concentration which is clearly attributable to turbulent mixing of the injected solution with the spinal fluid.<sup>1</sup> But there is as yet no convincingly demonstrated explanation for the slow but important fall which is responsible for the limited duration of the anesthesia. Koster, Shapiro, Warshaw and Margolick<sup>2</sup> have shown that it is possible to recover two thirds of an injected dose five minutes later by draining and washing out the subarachnoid space but that at the termination of anesthesia (about one hour later) less than 10 per cent is recoverable. Among the theories put forward at various times to explain the disappearance of the drug are fixation on nerve tissue, vascular absorption and hydrolysis to paraaminobenzoic acid. A possibility which has not been considered thus far is the formation of an acetylation product, either acetylprocaine or paraacetaminobenzoic acid.

The last two theories (hydrolysis and acetylation) were tested directly by analyzing samples of spinal fluid taken from patients under spinal anesthesia. The data obtained are summarized in table 1 and show that even when the anesthesia is wearing off about 97 per cent of the drug still present in the spinal fluid has undergone no change. About 2 per cent has been hydrolyzed and less than 0.5 per cent acetylated. These two theories may therefore be ruled out.

To check the validity of the other two theories, namely, the fixation and the vascular absorption theory, it is instructive to consider the results of analyses done on samples of blood taken at various intervals after the injection of procaine hydrochloride (table 2). It will be seen that although the concentration of procaine plus products of detoxication (total) is low (1 to 8 parts per million) the amount present in the 5 or 6 liters of circulating blood is not inconsiderable. In each case 5 to 10 per cent of the drug is accounted for. What is the fate of the

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1. Küstner, H., and Eissner, W.: *München. med. Wchnschr.* **77**:622, 1930. Koster, H.; Shapiro, A., and Leikensohn, A.: *Am. J. Surg.* **33**:245, 1936; Concentration of Procaine in Cerebrospinal Fluid of Human Being After Subarachnoid Injection, *Arch. Surg.* **37**:603 (Oct.) 1938. Koster, H.; Shapiro, A., and Warshaw, R.: Concentration of Procaine in Cerebrospinal Fluid of Human Being After Subarachnoid Injection, *ibid.* **39**:97 (July) 1939.

2. Koster, H.; Shapiro, A.; Warshaw, R., and Margolick, M.: Removal of Procaine from Cerebrospinal Fluid During Anesthesia, *Arch. Surg.* **39**:682 (Oct.) 1939.



remaining 90 per cent? It seems most probable that it is dispersed uniformly throughout all the body fluids, just as is the case with the closely related sulfanilamide.<sup>3</sup> In the last column of table 2 are presented the amounts of total products of detoxication estimated to be present in the total body water of each patient, the concentration being assumed to be equal to that in the blood. To verify the dispersion of the products of detoxication in this manner three experiments were done in which 300 mg. of paraaminobenzoic acid was injected intravenously into

TABLE 1.—*Hydrolysis and Acetylation in Spinal Fluid*

Patient	Time of Tap, Min.	Procaine Hydrochloride, Mg. per Ce. of Cerebrospinal Fluid	Percentage of Total Hydrolyzed	Percentage of Total Acetylated
Wa.....	34	1.60	2.4	0.11
Be.....	40	1.05	2.0	....
An.....	45	1.25	1.3	0.23
In.....	58	0.61	1.9	....
La.....	60	1.37	1.8	....
Ag.....	72	0.44	2.5	0.45

TABLE 2.—*Blood Analyses During Spinal Anesthesia*

Patient	Dose of Procaine Hydrochloride, Mg.	Minutes After Spinal Anesthesia	Proenine, Mg. per 100 Ce.	"Total," Mg. per 100 Ce.	"Total" Mg. per 50 Liters of Body Water
Ta.	150	30	.....	0.08	40
		60	.....	0.14	70
		90	.....	0.14	70
La.	300	60	0.000	0.60	300
Fr.	450	60	.....	0.85	425
Re.	300	41	0.013	0.40	200
		74	0.016	0.42	212
Se.	300	48	0.004	0.42	208
		98	0.003	0.53	264
Ir.	300	12	0.009	0.14	68
		60	0.010	0.39	196

human subjects and samples of blood were withdrawn at short intervals thereafter. The results showed that about 90 per cent of the substances had left the blood stream in five to ten minutes. This is the fraction to be expected if the amounts of paraaminobenzoic acid in all the body fluids were in equilibrium, since the blood volume is roughly 10 per cent of the body water.

3. So uniform is the distribution of sulfanilamide that it has been proposed by E. E. Painter (Am. J. Physiol. 129:744, 1940) as an agent for the experimental determination of body water. It is interesting to note the opinion of Dunlop<sup>9</sup> that in the dog procaine itself "is very rapidly removed from the blood by the tissues until equilibrium is reached between the tissues and the blood in respect to concentration of procaine."

It seems clear, therefore, that vascular absorption of the procaine is the primary reason for the fall in concentration in the spinal fluid. A residual 10 or 20 mg. of procaine may be recovered from the spinal fluid at the termination of anesthesia by the technic already mentioned.<sup>2</sup> While our findings do not elucidate the mechanism of the production of anesthesia, they indicate that if procaine is indeed "fixed" in the nerve tissue the total amount necessary must be relatively small.

Several authors have asserted that many of the striking phenomena accompanying spinal anesthesia are due to the presence of high concentrations of procaine in the blood:

The dosage of novocaine [procaine hydrochloride] is so high that the amount absorbed into the blood causes a general analgesic state, and the itching, drowsiness and stupidity of the patient, which has been described by various observers, is evidence of the action of the circulating drug on the sensory nerve endings in the skin and on the cortical cells of the cerebrum. . . . All the novocaine absorbed into the blood before this begins serves only to poison the patient and effects no useful purpose.<sup>4</sup>

Once the fact of [vascular] absorption is accepted, the untoward effects of spinal anesthesia might be explained on a simple pharmacologic basis. It will explain the nausea and vomiting (in the absence of abdominal manipulation and psychic causes), the intense itching occurring well above the level of anesthesia in some patients, the fall in pulse seen so frequently (probably due to the well-established depressant action of novocain on the heart musculature) and respiratory depression or failure by its action on the respiratory center. All these phenomena are known to occur after accidental intravenous injection of novocain.<sup>5</sup>

If procaine does indeed circulate in the manner indicated, it should respond to suitable chemical tests. The data in table 2 show that even after two or three times the usual dose of procaine hydrochloride the maximum concentration in the blood was only 0.016 mg. per hundred cubic centimeters. It is known that in experimental animals when rapid intravenous injection is used a dose of about 20 mg. per kilogram of body weight must be reached before toxic symptoms begin to be discernible. It should be appreciated that immediately after the injection the concentration of procaine in the animal's blood must approach 25 mg. per hundred cubic centimeters, or fifteen hundred times the highest concentration ever observed in the blood of a human being under spinal anesthesia. Moreover, if the drug is allowed to enter the blood stream slowly (as is the case in spinal anesthesia), as much as 400 mg. per kilogram of body weight may be administered with impunity.<sup>6</sup> Finally, attention is called to the report of MacDonald<sup>7</sup> that "the full spinal

4. Jones, W. H.: *Brit. M. J.* **2**:488, 1931. Wright, A. D., and Adams, A. W.: *ibid.* **2**:212, 1931.

5. Nowak, S. J. G.: *Anesth. & Analg.* **12**:232, 1933.

6. Hatcher, R. A., and Eggleston, C.: *J. Pharmacol. & Exper. Therap.* **8**:385, 1916.

7. MacDonald, A. D.: *Lancet* **1**:756, 1937.

dose" was injected directly into the veins of a human being "without ill effect."

In summary, we believe we are justified in stating that no appreciable concentration of procaine is built up in the blood during spinal anesthesia and that even if the concentration were several times the actual one it would not produce the effects attributed to it by the proponents of the toxic absorption theory.

Ever since the work of Hatcher and Eggleston<sup>8</sup> it has been accepted that the liver is charged with the function of detoxifying procaine. Goodman and Gilman<sup>9</sup> stated: "There is abundant proof that the liver is the site of destruction of the local anesthetics." Dunlop,<sup>9</sup> working with dogs, verified the important role of the liver and claimed that a Starling heart-lung preparation also had some slight activity. However, in a control experiment he found that blood was completely inactive.

TABLE 3.—*Hydrolytic and Acetylating Action of Human Blood on Procaine Hydrochloride in Vitro*\*

Time of Incubation	Percentage Hydrolyzed		Percentage Acetylated	
	Unheated Blood	Heated Blood	Unheated Blood	Heated Blood
5 min.....	52	24	..	..
30 min.....	98	79	..	..
21 hr.....	..	..	94	0

\* Fifty cubic centimeters of blood plus 1 cc. of 12 per cent sodium citrate solution was incubated at 37 C. with 3 mg. per hundred cubic centimeters of procaine hydrochloride; half of the blood was inactivated at 56 C. for three hours.

Our own experiments, limited thus far to blood of human beings and dogs, are not in agreement with this view. In table 3 we summarize a typical experiment carried out with a sample of normal human blood. The blood was incubated with procaine hydrochloride in a concentration of 3 mg. per hundred cubic centimeters. This is the concentration which would result if 150 mg. of procaine hydrochloride (one average dose) were diluted to 5 liters, the blood volume of the adult human being. In this experiment 50 per cent of the drug was detoxified in the first five minutes. In other experiments even greater activity was shown, but in one in which a concentration of 21 mg. per hundred cubic centimeters was taken, it required two hours of incubation to hydrolyze 72 per cent of the procaine. Three samples of canine blood were tested. Each sample showed definite activity, although far less than the human samples.

8. Goodman, L., and Gilman, A.: *Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students*, New York, The Macmillan Company, 1941.

9. Dunlop, J. G.: *J. Pharmacol. & Exper. Therap.* 55:464, 1935.

Can the discrepancy between our work and the work of Dunlop and Hatcher and Eggleston be reconciled? Dunlop described a single incubation experiment which "showed that blood alone has no effect on procaine." In a similar experiment with canine blood but with the use of our analytic methods, we found 30 per cent of the procaine destroyed. This difference of 30 per cent was perhaps within the limits of error of Dunlop's test, which he admitted was "only an approximate quantitative estimate." However, the use of smaller concentrations of drug leads to a much larger percentage of destruction. It is unfortunate that the relative insensitivity of the alkaline betanaphthol reagent apparently did not permit the use of lower concentrations.

"In order to test whether the blood fixes novocaine," Hatcher and Eggleston chose a far higher concentration (375 mg. per hundred cubic centimeters of the dog's blood) and reinjected the blood into the dog. The fact that the dog showed the symptoms to be expected if none of the drug had been destroyed was taken as evidence that the blood did not "fix" procaine. Hatcher and Eggleston apparently did not consider an enzymatic effect since they seem to have reinjected the blood promptly without any incubation. Obviously, this is a rough test at best and can indicate only the destruction of a large proportion of the procaine.

In the course of our experiments on detoxification *in vitro* it was noted not only that the procaine was hydrolyzed but that there was a diminution in the value for free amino groups, this process usually approaching completion in about twenty hours. Hydrolysis with hydrochloric acid, however, regenerated the free amino group. It is most probable that the process is an acetylation, but this is somewhat difficult to prove.<sup>10</sup> Confirming this assumption is the fact that dog's blood does not show this power of blocking the amino group. It is well known that *dogs do not acetylate aromatic amines*. However, the process seems to be relatively slow as compared with hydrolysis, and it is impossible even to guess whether the acetylation which takes place in the blood represents a major or a minor fraction of the acetylation which occurs in the body as a whole.

Separate experiments were carried out to determine whether or not the processes were of an enzymatic nature. It was found that heating the blood to 56 C. for three hours inhibited hydrolysis of the procaine, while the acetylating mechanism was completely destroyed. Addition of 0.3 per cent sodium fluoride likewise inhibited both mechanisms. These facts strongly suggest that the reactions are enzymatic in nature.

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10. It should be noted that an acetate concentration of only 0.65 mg. per hundred cubic centimeters is theoretically necessary for the complete conversion of all the paraaminobenzoic acid to the acetamino derivative. Preliminary experiments to determine whether the addition of sodium acetate would accelerate the reaction were inconclusive and had to be abandoned for lack of time.

TABLE 4.—*Urinary Excretion of Procaine Detoxication Products After Subarachnoid Injection of Procaine Hydrochloride*

Patient	Procaine Hydrochloride Injected, Mg.	Hours After Injection	Urine, Cc.	Total Detoxication Product, Mg.	Percentage Acetylated	Percentage Free	Procaine Hydrochloride, Mg.	Percentage Recovered (Cumulative)
Fr.	150	2	152	60.0	91.5	5.5	0.17	40.0
		4	61	16.4	98.5	1.5		71.0
		8	78	23.1	99.2	0.8		86.2
		24	255	11.8	98.6	1.4		96.4
		48	540	4.0	....	...		....
Total				118.6				99.0
Jn.	150	2	57	26.8	91.1	5.9	0.15	17.9
		4	11	11.11	98.2	1.8		25.3
		8	73	8.2	98.8	1.2		30.4
		24	295	75.0	99.1	0.9		80.6
		48	365	7.3	....	...		85.8
Total				120.55				87.0
Be.	150	2	89	0.12	100.0	0.0		0.25
		4	29	9.1	98.0	2.0		6.3
		8	133	89.6	98.1	1.9		66.2
		24	457	16.7	98.0	12.0		77.4
		48	780	12.8	....	...		85.9
Total				131.12				89.5
Ro.	150	6	122	97.6	96.0	4.0	....	63.2
		24	368	35.2	90.5	9.5		83.5
		48	404	5.0	....	...		....
Total				137.8				91.8
Gr.	150	6	1,110	77.6	100.0	0	....	51.8
		24	720	57.0	99.1	0.9		....
Total				134.6				89.6
Saz.	150	6	98	60.0	99.6	0.4	....	40.0
		24	360	47.6	98.5	1.5		....
Total				107.6				71.7
Say.	150	6	205	59.4	100.0	0	....	39.6
		24	1,100	75.2	100.0	0		89.9
		48	670	2.68	....	...		....
Total				137.28				91.6
Po.	150	6	700	79.2	98.6	1.4	....	52.9
		24	750	24.4	96.5	3.5		....
Total				103.6				69.2
Am.	150	6	76.5	99.6	93.6	6.4	....	66.5
		24	360	27.4	96.0	4.0		84.6
		48	585	3.5	....	...		....
Total				130.5				86.7
Ob.	150	6	223	115.0	98.4	1.6	0	76.7
		24	372	19.4	99.1	0.9		98.6
		48	905	1.18	....	...		....
Total				135.58				90.4
Sc.	300	24	192	124.0	97.9	2.1	0.26	41.3
		48	600	129.24	97.8	2.2		....
Total				253.24				84.4

TABLE 4.—*Urinary Excretion of Procaine Detoxication Products after Subarachnoid Injection of Procaine Hydrochloride—Continued*

Patient	Procaine Hydrochloride Injected, Mg.	Hours After Injection	Urine, Cc.	Total Dctoxication Product, Mg.	Percentage Acetylated	Percentage Free	Procaine Hydrochloride, Mg.	Percentage Recovered (Cumulative)
Ir.	300	1	44	4.84	85.0	15.0	0.39	1.6
		8	140	182.5	97.5	2.5		62.5
		24	370	50.2	98.7	1.3		79.3
		48	430	8.78	....	...		....
Total.....				246.62				82.2
As.	300	8	206	207.6	96.3	3.7	....	69.2
		24	176	36.4	94.8	5.2		81.3
		48	160	3.0	....	...		....
		Total.....				247.0		
Fr.	450	8	142	155.8	97.8	2.2	....	42.0
		24	330	190.8	96.6	3.4		83.7
		48	1,025	73.4	....	...		....
		Total.....				450.0		

It is at once obvious that if our experiments on the destruction of procaine by blood in vitro are accepted the experiments on the subject already in the literature must be reevaluated. Whether tests are carried out with organ mashers or by perfusion technics, the hydrolytic activity of the blood must be considered. It is also clear that the great difference between the activity of canine and human blood makes the value of experiments on dogs dubious. We have not had an opportunity to examine other species which might approximate man more closely. Nevertheless, we do not doubt that the liver also is capable of hydrolyzing procaine. It would be surprising if this great manufactory of esterase were incapable of doing this. The liver may in fact be the source of the esterase present in the blood.

For measuring the rate of excretion of the drug postoperative samples of urine were collected by means of an indwelling catheter. A pre-operative sample was also taken to insure the absence of any possible interfering substances due to earlier medication. The first result to be noted is the practical absence of procaine in the urine (table 4). This, however, should occasion no surprise, as it is known that even shortly after the injection nearly all the drug present in the blood is already detoxified. Although procaine itself is practically absent from the urine, nevertheless the detoxification products are found in quantities corresponding to about 90 per cent of the injected drug. This is a relatively high percentage, considering the small quantity of drug and the manifold biologic and technical factors which might lead to incomplete recovery. Whether any portion of the drug is excreted in feces or sweat or by any other route has not been investigated.

The exact chemical composition of the products of detoxification is difficult to determine, but fractionation at varying  $p_H$ 's leads us to believe

that about 2 per cent is excreted as paraaminobenzoic acid and about 30 per cent as paraacetaminobenzoic acid, the remainder being made up of paraacetaminobenzoyl glycine and paraacetaminobenzoyl glycuronate.

#### SUMMARY

By means of new chemical techniques it is shown that procaine within the subarachnoid space remains essentially unchanged. The fall in concentration of procaine, which is responsible for the wearing off of anesthesia, is due to vascular absorption.

Once in the blood stream procaine is rapidly hydrolyzed (detoxified) by an enzyme.

There is also a less active enzyme which acetylates the free amino group.

At no time is there any appreciable trace of procaine in the blood; hence, the cause of various "toxic" effects which have been attributed to a procainemia must be sought elsewhere.

The products of detoxication leave the blood stream rapidly until equilibrium is approached between the blood and all the other tissues.

Nearly all the injected procaine (90 per cent on the average) is excreted in the urine, but only in the form of products of detoxication more or less equally divided between paraacetaminobenzoic acid, paraacetaminohippuric acid and paraacetaminobenzoyl glycuronate.

40 Maple Street.

# THORACOABDOMINAL GUNSHOT WOUNDS

## A REVIEW OF EIGHTY-FOUR CASES

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Thoracoabdominal gunshot wounds are grave injuries which must be carefully studied and energetically treated. A penetrating projectile has no respect for fascial planes or divisions between body cavities; hence a combined lesion must be considered in all wounds of the lower portion of the thorax and the upper portion of the abdomen. Because of the great physiologic difference in the character of the abdominal and the thoracic cavity, injury to both as occurs in a penetrating wound contributes more profoundly to the patient's shock than injury to either of the cavities alone.

Thoracoabdominal penetrating wounds are common lesions during warfare. This type of lesion constituted 9 per cent of thoracic wounds and 12 per cent of abdominal wounds seen at the casualty-clearing stations of the British Expeditionary Forces in World War I according to MacPherson and associates,<sup>1</sup> Taylor<sup>2</sup> and Wallace and Fraser.<sup>3</sup> Jolly<sup>4</sup> found that 11 per cent of abdominal wounds in evacuation hospital units during the Spanish civil war were combined lesions. Heyd<sup>5</sup> reported that 10 per cent of the patients with wounds of the chest had wounds of the diaphragm and that 12 per cent of the patients with abdominal wounds seen by him in the American Expeditionary Forces of World War I had concomitant injuries of the chest. Lee,<sup>6</sup> however,

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1. MacPherson, W. G.; Wallace, C.; Bowlby, R. A., and English, C.: *Official History of the War Medical Services: Surgery of the War*, London, His Majesty's Stationery Office, 1922, vol. 1.

2. Taylor, G.: *Abdominothoracic Wounds of Warfare*, *Brit. M. J.* 2:131-134 (Aug. 2) 1919.

3. Wallace, C., and Fraser, J.: *Surgery at a Casualty Clearing Station*, London, A. & C. Black, Ltd., 1918, pp. 207-210.

4. Jolly, D. W.: *Field Surgery in Total War*, New York, Paul B. Hoeber, Inc., 1941.

5. Heyd, C. G.: *Thoraco-Abdominal Injuries: Some Technical Procedures Developed by the War*, *Ann. Surg.* 72:370-375, 1920.

6. Lee, W. E.: *Medical Department of the U. S. Army in the World War*, Washington, Government Printing Office, 1927, vol. 2, pp. 466-468.



found that only 4.6 per cent of all thoracic wounds had penetrated the abdomen in the American Expeditionary Forces of World War I.

For this study 84 cases of combined thoracoabdominal gunshot wounds were reviewed from the records of the Cook County Hospital and the Cook County Morgue. The patients in this study represent patients observed at these institutions during a four year period (1933 to 1937). Twenty-nine of these patients were treated at the Cook County Hospital; 55 were examined by the Cook County coroner's staff. Operation or postmortem examination was performed on all of the patients who died. Seventy-nine of these patients were wounded by rifle or revolver bullets in which all of the common calibers were represented. There were 5 shotgun wounds.

#### CLASSIFICATION

Several classifications of thoracoabdominal wounds have been described.<sup>7</sup> For this study it was found convenient to classify the wounds according to the clinical manifestations presented. When seen in the accident rooms of municipal hospitals during civil life or in the forward classification posts during warfare, the clinical manifestations of these wounds exhibit one of the following varieties: (1) shock (hemorrhage) syndrome; (2) thoracic (respiratory) syndrome; (3) peritoneal syndrome; (4) retroperitoneal syndrome.

*Shock (Hemorrhage) Syndrome.*—Massive hemorrhage is the characteristic finding in the group of patients showing the shock (hemorrhage) syndrome. In many of these patients penetration of the heart is found at autopsy (fig. 1 A). The patients die soon after being shot. When the aorta or the vena cava is penetrated, death also occurs rapidly. In some cases extensive laceration or pulpification of the liver, the lungs or the kidney gives rise to a rapidly fatal hemorrhage. Occasionally when a smaller vessel is severed the patient may live for several hours after being admitted to a hospital; it is only under such circumstances that any hope of successful therapy can be entertained. As has been noted in a previous paper,<sup>8</sup> the majority of wounds of the heart enter the lower middle or left anterior portion of the thoracic wall, and protection of this area would be effective in preventing many of such wounds.

7. (a) Gordon-Taylor, G.: Chest Surgery in War: Abdominothoracic Injuries. Brit. M. J. 1:862-864 (June 7); 898-901 (June 14) 1941. (b) Heyd.<sup>5</sup>

8. Hardt, H. G., Jr., and Seed, L.: Comparison of the Course and Direction of Fatal and Nonfatal Gunshot Wounds of the Chest, War Med. 2:623-634 (July) 1942.

In warfare also many of the patients die before they can be evacuated to a hospital. According to Duval,<sup>9</sup> during warfare at least 50 per cent of the patients with penetrating wounds of the thorax die soon after injury, in the aid posts or in the ambulance units. For this reason many of the cases of massive hemorrhage do not appear among cases reported from military hospitals during war.

*Thoracic (Respiratory) Syndrome.*—The majority of the wounds causing the thoracic (respiratory) syndrome penetrate the lower lobe of the right lung or the right costophrenic sinus, pierce the diaphragm

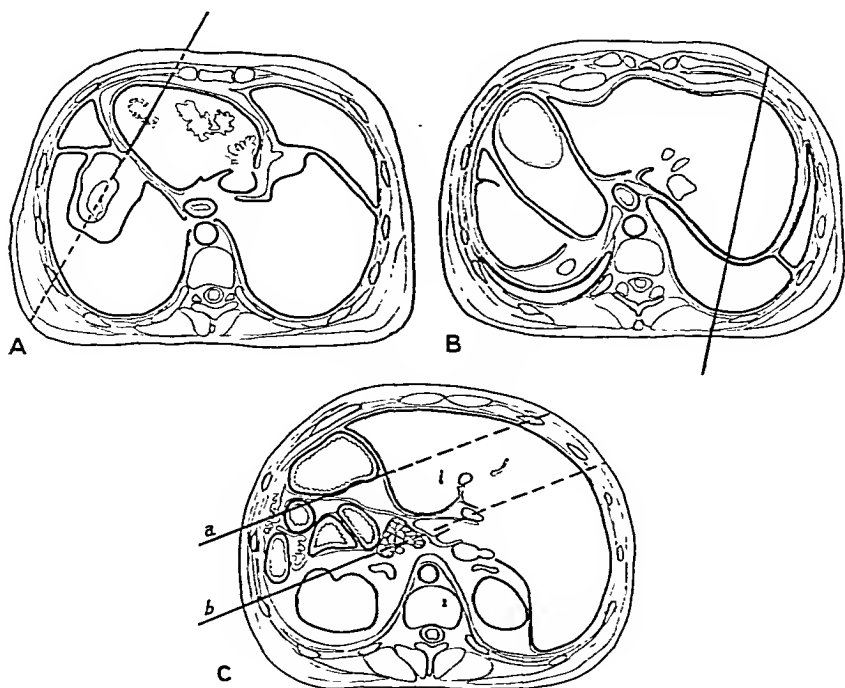


Fig. 1.—Typical courses of projectiles: *A*, causing the shock (hemorrhage) syndrome; *B*, causing thoracic (respiratory) syndrome; *C*, (*a*) causing peritoneal syndrome and (*b*) causing retroperitoneal syndrome.

and cause a tunneling or grooving lesion of the dome of the liver (fig. 1 *B*). Right-sided hemothorax is frequently present. Hepatic bleeding is usually not excessive; according to Heyd<sup>5</sup> hemorrhage is usually arrested by the time a laparotomy can be done. Of course, in some cases fissuring and shattering of the liver cause profuse and constant hemorrhage, but the condition is then classified under the hemorrhage syndrome. A similar clinical picture is occasionally present in

9. Duval, P.: *War Wounds of the Lungs: Notes on Their Surgical Treatment at the Front*, New York, William Wood & Company, 1918.

wounds of the lower part of the left lung and the spleen. The clinical course of these wounds is similar to that of penetrating wounds of the right side of the thorax. Early and uneventful recovery usually follows. Occasionally hemothorax must be treated by aspiration and replacement with air, but rarely is any operative therapy necessary. Wounds of the right hypochondrium were described as the most benign of any of the abdominal wounds by Keogh<sup>10</sup> (fig. 2).

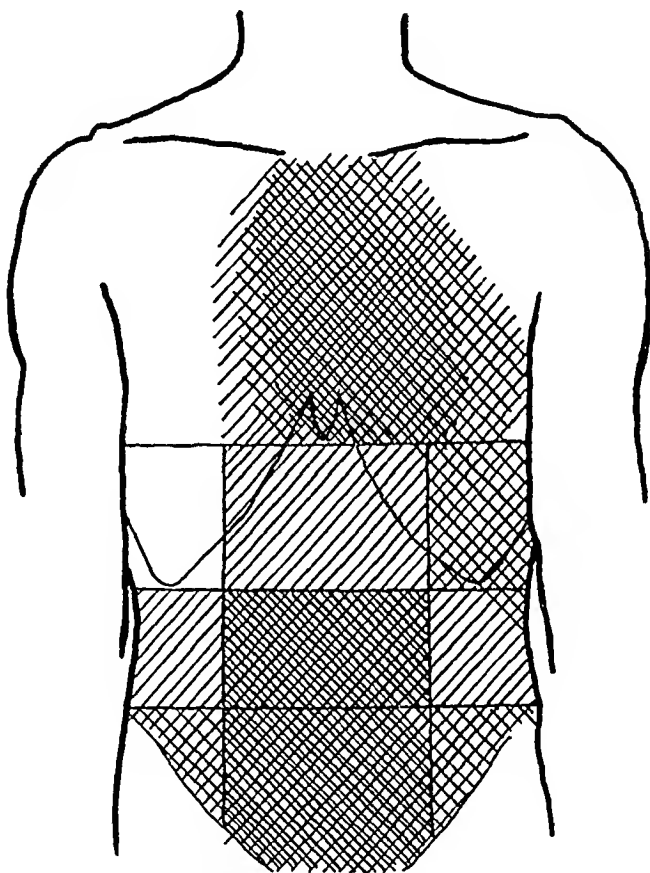


Fig. 2.—Most vulnerable areas on the anterior surface of the trunk. The darker areas indicate those in which wounds have a graver prognosis (abdominal areas after Keogh<sup>10</sup>).

*Peritoneal Syndrome.*—The peritoneal syndrome is characterized by the penetration of hollow viscera. The lower lobe of a lung or the costophrenic sinus on either side of the thorax is penetrated, and the stomach or other portions of the intestinal tract are perforated (fig. 1 C). In addition, there is often penetration of one or more of the solid organs

10. Keogh, A.: *Medical and Surgical Therapy*, New York, D. Appleton and Company, 1918, vol. 3, pp. 377-383.

in the peritoneal cavity or in the retroperitoneal region. The clinical manifestations are those of peritoneal reaction seen in perforation of any hollow viscus. Shock, abdominal tenderness, boardlike rigidity, nausea and occasional vomiting are usually present. Peristaltic sounds are absent; and distention soon appears. In these cases immediate operative repair is required; otherwise the subsequent infection becomes overwhelming.

*Retroperitoneal Syndrome.*—A small portion of abdominothoracic gunshot wounds present a clinical picture which has been called a retroperitoneal syndrome by Jolly.<sup>4</sup> The principal wound is found in the mesentery and the retroperitoneal organs (fig. 1 C). Pallor, weakness, feeble pulse, low blood pressure and other signs of shock are present. There is little pain and no evidence of peritoneal reaction. The shock becomes more profound, and death ensues. The exact causation of this syndrome is not clear. There is insufficient bleeding to account for the shock present. Jolly<sup>4</sup> expressed the opinion that the manifestations are due to damage to the splanchnic nerves.

#### WOUNDS OF INDIVIDUAL ORGANS

*Frequency.*—The frequency with which individual organs were penetrated is given in table 1. Not uncommonly a projectile penetrated the costophrenic angle; for this reason no thoracic organ was penetrated in some cases. The order of frequency varies somewhat from the rate of frequency reported by Jolly.<sup>4</sup> In this series there were more wounds of the kidney and fewer wounds of the spleen, so that the frequency of injury of these two organs is the reverse of that reported by Jolly.<sup>4</sup>

*Thorax.*—Heart: The heart was injured in 21 cases (25 per cent). In 17 of these there was complete penetration of at least one wall, and in 1 the myocardium was deeply lacerated. All of these patients died before they could be admitted to a hospital. In 3 cases there was simple contusion or grooving of the myocardium; the patients lived three hours, twelve hours and twenty-four hours respectively after being admitted to a hospital.

Since most of these patients die before they can be admitted to a hospital, they can rarely be treated with any hope of success. Occasionally a grooving or saucerizing lesion of the myocardium can be successfully sutured if recognized early. Elkin,<sup>11</sup> Bigger,<sup>12</sup> Griswold and Maguire<sup>13</sup> and others have recorded numerous instances of successful

11. Elkin, D. C.: The Diagnosis and Treatment of Cardiac Trauma. *Ann. Surg.* **114**:169-185 (Aug.) 1941.

12. Bigger, I. H.: The Diagnosis and Treatment of Heart Wounds, *South. M. J.* **33**:6-11 (Jan.) 1940.

13. Griswold, R. A., and Maguire, C. H.: Penetrating Wounds of the Heart and Pericardium, *Surg., Gynec. & Obst.* **74**:408-418 (Feb. 15) 1942.

repair of a penetrated heart. In the majority of cases in which treatment was successful, the wounds were caused by a knife or an ice pick. These weapons cause small wounds which penetrate only one cardiac wall and in most cases do not penetrate the pleural cavity at all. In gunshot wounds there is usually complete penetration of the heart and frequently an opening into the pleural cavity which allows massive hemorrhage to progress to the point of exsanguination. Cardiac tamponade, a common finding in knife wounds, is not frequently seen in gunshot wounds. The difference in these two types of lesions has been previously described by Bigger.<sup>12</sup>

Lungs: A lung may sustain a simple drill hole type of wound from a penetrating bullet, or it may be extensively lacerated and contused.

TABLE 1.—*Frequency with Which Individual Organs Were Penetrated by Gunshot Wounds*

	Organ	Cases	Percentage
Thorax	Right lung.....	23	27.4
	Left lung.....	32	38.1
	Heart.....	21	25.0
Abdomen	Liver.....	59	70.3
	Stomach.....	30	35.7
	Kidney.....	17	20.2
	Large intestine.....	13	15.4
	Spleen.....	12	14.3
	Pancreas.....	12	14.3
	Small intestine.....	8	9.5
	Adrenal gland.....	4	4.7
	Aorta.....	4	4.7
	Vena cava inferior.....	4	4.7
	Gallbladder.....	1	1.2
	Innominate vein.....	1	1.2

Most injuries of the latter type are caused by shell fragments. The track of the projectile is usually surrounded by a zone of parenchymal hemorrhage. In some cases profuse bleeding into the parenchyma of the lung or the bronchial tree occurs.<sup>9</sup> Hemothorax or hemopneumothorax is usually present. If these are minimal in extent, no active therapy will ordinarily be required; moderate or large accumulations of blood should be treated by aspiration and replacement with air. When there is extensive damage to the lung in addition to hemothorax or a large intrapleural foreign body is present, thoracotomy and repair of the lung are the treatment of choice. Pneumothorax ordinarily is desirable to secure adequate rest for the lung to promote healing. Occasionally, however, a valvelike wound may allow entrance of air but prevent its exit; constantly mounting pleural pressure or tension pneumothorax will result and may cause sufficient respiratory embarrassment to produce death unless effectively decompressed. Open pneumothorax

must be immediately closed. Operation is also indicated for wounds of the intercostal or internal mammary vessels. Large ragged wounds of the wall of the chest and compound fractures of the ribs will require débridement, cleansing and repair. Mediastinal emphysema will occasionally require an incision above the episternal notch to relieve pressure in the mediastinum and the neck. The care of penetrating wounds of the thorax has been more completely reviewed in a previous paper.<sup>14</sup>

*Diaphragm.*—Wounds of the diaphragm as seen in civilian life are small and are usually located in the sloping muscular portion of the organ. Wounds of the muscular portion of the diaphragm are considered more benign than those of the tendinous portion.<sup>7a</sup> In warfare also most of the wounds are small; however, some caused by large shell fragments reach sizable dimensions. The characteristic clinical finding with lesions of the diaphragm is a thoracic character of respiration with a catch, spasm or hiccup at the height of inspiration and pain referred to the scapula or the clavicle. Herniation of abdominal viscera into the thoracic cavity may occur immediately following a wound of the diaphragm. This usually occurs in those wounds in which a sizable rent is present. Diaphragmatic hernia occurring subsequent to thoracoabdominal wounds is a fairly common occurrence; it was estimated by Lee<sup>6</sup> to occur in approximately 10 per cent of thoracoabdominal gunshot wounds. Hernia of traumatic origin is almost invariably on the left side. Hedbloom<sup>15</sup> found that approximately one third of all diaphragmatic hernias in his series were of traumatic origin. Approximately half of these were due to penetrating wounds, the majority of which were caused by bullets. Many small wounds of the diaphragm heal satisfactorily spontaneously; large wounds require repair. Sauerbruch<sup>16</sup> and others have expressed the opinion that repair of a lacerated diaphragm is not so vital to the maintenance of respiratory equilibrium as was formerly thought. On some occasions it is technically difficult to repair a laceration of the diaphragm through an abdominal incision; consequently a transpleural approach will frequently be necessary.

*Abdominal Cavity.*—Liver: Because of the large size and the prominent position of the liver, it is injured more frequently by thoracoabdominal gunshot wounds than any other organ. In this series it was involved in 59 cases (70.1 per cent). Considerable variety of lesions are found among gunshot wounds of the liver. In some cases a groove

14. Hardt, H. G., Jr., and Seed, L.: Gunshot Wounds of the Chest: A Review of Two Hundred and Eighty Cases, *Arch. Surg.* 44:779-788 (May) 1942.

15. Hedbloom, C. A.: Diaphragmatic Hernia, *Ann. Int. Med.* 8:156-176 (Aug.) 1934.

16. Sauerbruch, F., and O'Shaughnessy, L.: *Thoracic Surgery*, New York, Longmans, Green & Co., 1937, pp. 346-347.

or trenchlike injury is found; in others a tunneling of the organ is present. Occasionally in association with these wounds fissures of varying size radiate from the lesion. In some cases shattering or pulpification of an entire lobe or section of the organ is found. Wounds of the last-named type are found in those patients who die soon after the injury. The explanation of these varieties of injury can be found in the type, the character and the penetrating force of the missile. The clinical findings vary with the type and the extent of the damage present. In cases of severe shattering lesions the findings are those of profuse hemorrhage; mild lesions may be symptomless. The clinical manifestations are often obscured by the presence of damage to other viscera. Jaundice appearing soon after injury is usually temporary; jaundice developing late in the course of an injury often indicates infection according to Gordon-Taylor.<sup>7a</sup> Secondary hemorrhage from wounds of the liver is often severe and is frequently fatal. Laparotomy is indicated for wounds involving the liver when bleeding is progressive and when a large foreign body is present in the substance of the liver. The bleeding is controlled by packing or suture.

**Spleen:** In this series the spleen was penetrated in 12 cases (14.3 per cent). Wounds of the spleen resemble those of the liver. They are usually grooved or trenchlike but may be shattering or pulpifying. Wounds of the pedicle frequently give rise to fatal hemorrhage. Clinical findings are similar to those in cases of wounds of the liver. Wounds of the spleen are seldom found to be the only abdominal visceral injury. With some of the less severe wounds of the organ suture may be possible but many require splenectomy. Jolly<sup>4</sup> was enthusiastic over the results of splenectomy observed by him in the Spanish civil war. Transthoracic splenectomy has been frequently performed with success by Gordon-Taylor.<sup>7a</sup>

*Hollow Viscera.*—The stomach, the colon or the small intestine may be penetrated in thoracoabdominal gunshot wounds. In this series the stomach was the most frequently injured, being penetrated in 30 cases (35.7 per cent). The transverse colon or the splenic or the hepatic flexure was pierced in 13 cases (15.4 per cent), while the small intestine was perforated in 8 cases (9.5 per cent).

The type of perforation of these hollow viscera depends on the course and direction and the type of penetrating missile. A bullet or shrapnel usually causes either penetration of both walls or, when penetrating at an angle or striking an edge of the organ, tearing of a single area of one wall. Wounds caused by shell fragments or shotgun discharges usually tear a large section of the organ away or completely divide it. Wounds of the greater or lesser curvatures of the stomach may involve

the large blood vessels in the mesentery, causing profound and even fatal hemorrhage. This may also occur in wounds of the mesocolon or the mesentery of the small intestines. The clinical findings are those of general peritonitis. Shock, abdominal rigidity, localized tenderness, nausea and absence of peristaltic sounds are usual. Vomiting is often present when the stomach is involved. Laparotomy is indicated when penetration of a hollow viscus is suspected. Obviously the prognosis of these wounds is better for those patients who are operated on soon after infliction of their wound. Simple suture of the perforations should be done whenever possible. This has been advocated by Bailey,<sup>17</sup> even when it entails considerable narrowing of the intestinal lumen. The mortality associated with suture is considerably less than that associated with resection; consequently resection should be done only in those cases in which there is no reasonable alternative.

*Extraperitoneal Organs.*—Pancreas: The pancreas was penetrated in 12 cases (14.3 per cent) in this series. Pancreatic lesions are rarely recognized preoperatively. Certainly many of them are fatal. This may be due to hemorrhage from the many large vessels in the vicinity; it may occur with the retroperitoneal syndrome described earlier, or extensive fat necrosis may be a contributing factor to the fatal outcome. Suppurative gangrenous pancreatitis may produce death in twenty-four hours in cases of pancreatic wounds according to Heyd.<sup>5</sup> It is difficult to determine whether any pancreatic lesions tend to simple regression.

Kidney: In this series the kidney was injured in 17 cases (20.2 per cent). The kidney may be contused from projectiles passing in the vicinity of the organ. This may cause hematuria (which is temporary) but few or no complications. A projectile may cause a tunnel-like perforation or bisect or pulpify the organ. The character of the wounds depends on the type and the energy of the penetrating missile. Injury to other organs is usual. The prognosis is particularly grave when the colon is perforated in addition to the kidney. Perforation of the renal pedicle or the calices is usually fatal. The diagnosis is established from the course of the wound and the presence of perirenal effusion and hematuria. Operation is indicated in the presence of large perirenal effusion, large foreign bodies and persistent bleeding. The usual surgical procedures are packing, suture and nephrectomy. Occasionally repair of a kidney through a lesion in the diaphragm is possible according to Swan.<sup>18</sup> Heminephrectomy is rarely indicated.

17. Bailey, H.: *Surgery of Modern Warfare*, Baltimore, Williams & Wilkins Company, 1941, vol. 1, p. 209.

18. Swan, R. H. J.: *Injuries of the Kidney*, Brit. J. Urol. **12**:161-176 (Sept.) 1940.



Adrenal Gland: The adrenal gland was penetrated in 4 cases (4.7 per cent). There have been few if any publications in the literature discussing gunshot wounds of this organ. In none of the cases in this series could any evidence of adrenal insufficiency be found.

#### COMBINATIONS OF VISCERA INJURED

Although many thoracoabdominal wounds exhibit an infinite variety in the combinations of organs and structures penetrated, certain combinations of wounds occur with a greater frequency. In table 2 are listed the more common combinations of wounds observed. These correspond fairly closely with the combinations observed by Lockwood and Nixon,<sup>19</sup> with the exception that those observers were in hospitals during warfare and therefore failed to see many of the rapidly fatal wounds involving the heart which were seen in this series.

TABLE 2.—*Frequency with Which Combinations of Viscera Were Injured by Gunshot Wounds*

Combination of Viscera	Cases	Percentage
Lung or costophrenic sinus and liver.....	17	20.2
Lung, heart and liver.....	7	8.3
Lung or costophrenic sinus, liver and stomach.....	6	7.1
Lung and stomach.....	4	4.7
Lung, liver and kidney.....	4	4.7
Heart and liver.....	4	4.7
Lung and spleen.....	3	3.5

#### DIAGNOSIS

In many cases, in which both a wound of entrance and one of exit are present, the diagnosis is obvious and the organs penetrated can be readily ascertained. In some cases, in which only an entrance wound is present, it may be difficult to determine whether a thoracoabdominal wound has been inflicted. In these cases a knowledge of the position of the patient when the wound was received and of the general direction of the adversary may be of considerable value. This has been emphasized by Meyer and Shapiro.<sup>20</sup> Information on the course of the bullet can often be obtained from a careful examination of the entrance wound. It is sometimes difficult to determine whether a wound is entirely thoracic or whether the abdominal cavity has been entered. Abdominal

19. Lockwood, A. L., and Nixon, J. A.: War Surgery of the Chest, Brit. M. J. 1:104-109 (Jan. 26) 1918.

20. Meyer, K., and Shapiro, P. F.: Treatment of Abdominal Injuries: Collective Review, Internat. Abstr. Surg. 66:245-257, 1938; in Surg., Gynec. & Obst., May 1938.

rigidity is frequently present with wounds of the lower part of the thorax; however, it is usually unilateral, while bilateral rigidity is often found with abdominal wounds. The rigidity with thoracic wounds is usually intermittent with respiration, while with abdominal wounds the rigidity is continuous. Vomiting and gaseous eructations are not unusual with abdominal wounds and are rare with purely thoracic wounds. When it is difficult to determine whether a wound is entirely thoracic, and also generally in cases of thoracoabdominal gunshot wounds, a flat plate roentgenogram of the upper part of the abdomen and the lower part of the thorax or fluoroscopic examination is of great value. By the position of the projectile, if this can be visualized, its course can often be determined. The presence of pneumothorax or hemothorax will establish the fact that the pleural cavity has been penetrated. The finding of air under the diaphragm confirms the presence of injury of a hollow viscus. Hemopericardium can readily be detected, and hematomas, tension pneumothorax and other abnormalities are often demonstrable.

In patients admitted to the hospital with the hemorrhage syndrome the presence of severe shock makes the diagnosis obvious; occasionally it may be fairly difficult to determine whether the bleeding is in the thoracic or the abdominal cavity. In most cases, however, hemothorax or hemopericardium can easily be detected by ordinary physical examination. If these are absent, it is reasonable to assume that bleeding in the abdominal cavity is present.

In cases of thoracoabdominal wounds of the thoracic type the location of the wound and the benign character of the clinical picture (providing bleeding is not excessive) are easily recognized. The differential diagnosis between purely thoracic wounds and combined wounds will be of value in those cases in which there is some doubt concerning the possibility of perforation of a hollow viscus.

The peritoneal syndrome is characterized by the readily recognizable feature of general peritonitis in almost every instance and should cause no difficulty.

The retroperitoneal syndrome will be characterized by profound shock which is progressive. Careful search will reveal no evident profuse bleeding. Peritoneal reaction will be minimal. The diagnosis can be made from the course of the wound and the exclusion of excessive bleeding and peritonitis in the presence of shock with little pain.

#### PROGNOSIS

Of the 29 patients admitted to Cook County Hospital with thoracoabdominal gunshot wounds, 13 recovered (mortality of 56 per cent). Projection of their cases with those obtained from the Cook County

Morgue (in some of the latter, treatment was carried out in other hospitals) reveals that approximately one third of the patients die immediately or at least soon after injury, that one third die after having received treatment in a hospital and that one third recover. Mortality rates reported by various observers vary from the 20 per cent quoted by Saint<sup>21</sup> to 75 per cent in the forward areas in warfare. The mortality rate will certainly vary greatly with the type of warfare, the length of time after injury and the facilities for therapy available. Wounds involving the structures in the right hypochondrium and lower right part of the thorax carry a favorable prognosis. Wounds of the lower left and lower middle portions of the anterior part of the chest will usually be rapidly fatal from penetration of the heart. Wounds of hollow abdominal viscera have a much higher mortality than wounds of solid viscera.<sup>22</sup> Among wounds of the hollow viscera the prognosis is better for wounds of the stomach than for intestinal wounds; for wounds of the small intestine the mortality is lower than for wounds of the colon. Penetration of both leaves of the diaphragm has a high mortality.

Lilienthal<sup>23</sup> expressed the opinion that wounds penetrating from abdomen to thorax have a higher mortality than those passing from thorax to abdomen. The high mortality in the hospital from abdominal wounds of this type is due mainly to uncontrollable peritonitis which persists and causes death in many cases in which skilful repairs have been made. It is hoped that the local use of sulfonamide compounds in the peritoneal cavity will aid in the control of such infection sufficiently to cause a marked lowering of this mortality.

#### CAUSE OF DEATH

The cases herein reported cannot yield a true cross index of thoraco-abdominal gunshot wounds, since the cases from the hospital do not include the cases in which death occurred before hospitalization could be effected and the coroner's cases do not include the cases from other hospitals in which recovery took place. However, an approximation of the true proportions can be obtained by projection of the figures available here. These figures reveal that approximately one third of all patients die from profound hemorrhage before active therapy can be instituted in a hospital. Approximately one third of the patients die in spite of active therapy in the hospital, and one third recover.

21. Saint, cited by Taylor.<sup>2</sup>

22. Rippey, E. L.: Management of Perforating Gunshot Wounds of the Abdomen, *South. Surgeon* **10**:441-450 (June) 1941. Gordon-Taylor, G.: *Abdominal Injuries of Warfare*, Bristol, John Wright & Sons, Ltd., 1939.

23. Lilienthal, H.: *Thoracic Surgery*, Philadelphia, W. B. Saunders Company, 1926, vol. 2, pp. 568-570.

In the first group hemorrhage frequently arises from the heart or other portions of the central vascular tree, but occasionally persistent bleeding from a smaller vessel is the causative factor. In the latter instance the patient often lives several hours after being admitted to the hospital before he dies. Thirty-seven patients in this series died from hemorrhage.

Infection is by far the most common cause of death in those patients who have received active therapy in the hospital. There were 21 deaths from infection in this series. Death usually occurs between the second and the fifth day in the hospital. Infection may be present in any of the body cavities penetrated, and it is interesting to note that in the majority of cases infection is present in both cavities penetrated. The

TABLE 3.—*Major Source of Bleeding in Thirty-Seven Deaths from Hemorrhage*

Source of Hemorrhage	Cases	Hours Patient Lived After Admission to the Hospital
Heart (21 cases)		
Heart penetrated.....	17	0
Myocardium lacerated.....	1	0
Myocardium contused.....	1	3
Saucerized ventricle.....	1	12
Grooved ventricle.....	1	24
Aorta (abdominal).....	4	0, 0, 0, 5
Lung.....	4	0, 0, 4, 48
Kidney.....	3	0, 5, 6
Liver (shattered).....	2	0, 6
Right innominate vein.....	1	0
Splenic artery (large branch).....	1	19
Hematoma in the anterior mediastinum.....	1	6

findings of late general peritonitis and pyohemothorax are usually obvious.

Seven patients in this series died soon after operation. In cases of this kind it is unfortunately impossible to determine with certainty which of the patients will be able to withstand the additional shock of operation and which will not. It is hoped that improvements in pre-operative preparation of the patient and utilization of whole blood and plasma in the operating room will aid in reducing the number of post-operative deaths. Large amounts of blood and plasma (1,000 to 2,000 cc.) may be necessary to restore the patient's blood volume in the operating room.<sup>24</sup>

Three patients died in deep shock six to ten hours after injury. Postmortem examination failed to reveal sufficient bleeding to explain the shock present. These patients all had severe retroperitoneal wounds,

24. Storck, A. H.: Gunshot Wounds of the Abdomen. Surg., Gynec. & Obst. 74:425-427 (Feb., no. 2A) 1942.

and for want of a more adequate explanation of the cause of death we place their wounds in the category of retroperitoneal syndrome described by Jolly.<sup>4</sup> It is interesting to note that the pancreas was penetrated in each of these cases.

Two patients died from paralytic ileus. One death occurred twenty-six days after injury and the other three and a half days after the patient was wounded.

#### TREATMENT

Wounds of the right lower part of the thorax and the right hypochondrium frequently require no operative therapy. Right hemothorax may be treated by aspiration and air replacement if sizable. Operation is indicated only when a large foreign body is present or when there is considerable damage to the organ with continued bleeding. These indications are equally true for both the lower lobe of the right lung and the liver.

If a wound of the heart is suspected from the site of the wound and the clinical findings, immediate exploration is imperative. If early operation is done on patients who reached the hospital, the bleeding from a grooving or saucerizing lesion of the myocardium can be successfully arrested. Unfortunately most of the lesions will have penetrated the cardiac wall and the patient will fail to reach the hospital alive.

Wounds with perforation of hollow viscera require laparotomy as soon as the patient's condition warrants. It has been demonstrated accurately that the prognosis is much better for those patients on whom operation is done early. Exploration of the spleen is indicated in the presence of continued bleeding, and this holds true also for the kidney. It may be possible to examine the spleen through the pleural cavity if this cavity must be entered for other reasons. This is advocated by Jolly<sup>4</sup> and Gordon-Taylor.<sup>7a</sup> Transperitoneal exploration of the kidney is not recommended.

It may frequently be difficult to determine whether to perform an exploratory operation first on the thoracic or on the abdominal cavity. Duval<sup>9</sup> expressed the opinion that the pleural cavity should be operated on first: (1) if open pneumothorax is present; (2) if a large intrapleural foreign body is found, or (3) if a large amount of parenchymal damage with continued bleeding from the lung is present. Jolly<sup>4</sup> stated his belief that transpleural laparotomy is indicated when a large diaphragmatic perforation is present or when the course of the projectile is known to be in the upper part of the abdomen. The fact that when infection occurs both the pleural and the abdominal cavity are involved in a majority of cases should indicate that careful suture of the diaphragm should be done if at all possible.

Autotransfusion of blood in hemothorax cavities as advocated by Brown<sup>25</sup> should be done only in carefully selected instances of thoraco-abdominal wounds, since penetration of abdominal structures may allow infection to enter the pleural cavity. The adequate use of sulfonamide compounds orally and in the thoracic as well as the peritoneal cavity in those cases in which a hollow viscus has been penetrated may be helpful in controlling the infection present. It is to be hoped that a large number of patients with wounds of types that in the past have proved fatal because of infection will be saved in the future by the use of sulfonamide compounds.

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25. Brown, A. L., and Debenham, M. W.: Autotransfusion: Use of Blood from Hemothorax, *J. A. M. A.* **96**:1223-1225 (April 11) 1931.

## PROGRESS IN ORTHOPEDIC SURGERY FOR 1941

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE  
AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

(Concluded from Page 1671)

### XVI. CONDITIONS INVOLVING THE FOOT AND ANKLE

*Foot Imbalance.*—Schwartz and Heath<sup>605</sup> conclude from clinical observation and laboratory investigation of the foot in action: (1) that perfect alinement between the foot and the leg can be maintained without muscle support; (2) that unusual development of the intrinsic and extrinsic muscles of the foot and the leg does not prevent pronation in stance and locomotion; (3) that the presence or the absence of pronation can be explained on the basis of functional characteristics of the os calcis and the cuboid bone and their physical relation to the astragalus and the tibia. (A neutral or varus position of the os calcis does not permit pronation of the foot.)

These conclusions are in harmony with the observations of Morton<sup>606</sup> and others that foot balance depends on two factors: (1) structural stability, by which is meant the arrangement of the bones and the ligaments of the foot which enables it to provide a rigid base of support for superimposed body weight; (2) postural stability, by which is meant that quality by which the center of transmitted weight is constantly maintained in a balanced position over the astragalus with each shift of the body weight.

According to these authors both true structural and true postural stability depend on the maintenance of a parallel between the axis of weight bearing of the os calcis and the tibia. They therefore conclude that muscle exercises are contraindicated in the treatment of pronation and that treatment is limited to means which will maintain a neutral or varus position of the os calcis. [ED. NOTE: While we agree entirely with the basic conclusions of Schwartz and Heath, we feel that the long extrinsic muscles of the foot across the subtalar joint do play a definite role in maintaining the leg in a functionally vertical position over the os calcis with each shift of the body weight and that the desir-

605. Schwartz, R. P., and Heath, A. L.: Foot Function Correlated with Anatomic, Clinical and Laboratory Data, New York State J. Med. **41**:447-451 (March 1) 1941.

606. Morton, D. J.: Functional Disorders of Foot and Their Treatment, Arch. Phys. Therapy **22**:651-655 (Nov.) 1941.

ability of establishing adequate strength and tone in the long muscles cannot be ignored in the treatment of pronated feet.]

The authors emphasize also a fundamental fact when they point out that the distorting influence of pronation on the cartilaginous skeleton of the child's foot results in changes in shape and structure of the bones of the foot, particularly the os calcis, which are so predetermined as to express the characteristics of pronation in adult life. The correction of faulty foot posture in childhood will eliminate a large part of the foot disorders of adult life. R. L. Jones,<sup>607</sup> an anatomist, using an ingenious apparatus for measuring the mechanics of the foot, also concludes that the plantar ligaments and the short plantar muscles bear the greater part of the burden of supporting the longitudinal arch of the foot and that the long leg muscles do about 15 to 20 per cent of the work. He does concede, however, that the long muscles have a definite role in maintaining the leg in a balanced position over the foot and in this way influence the distribution of weight. An unequal distribution of weight over the foot is one of the fundamental causes of the breaking down of the structural stability, and Jones's contention that the long muscles of the foot (leg) are completely unimportant in supporting the longitudinal arch seems to fail of proof. On the other hand, a preponderance of evidence based on clinical experience does support his claim that a depressed longitudinal arch cannot be elevated by exercises of muscles alone. Finally, Jones makes the flat statement that commercial arch supports are of little value as elevators of the arches of the foot. [ED. NOTE: This claim is well founded, since such supports seldom meet all of the requirements in a truly imbalanced foot; it is not true, however, of properly designed and properly fitted supports made to meet the needs of the individual patient.] Wiles<sup>608</sup> has written an interesting article covering much ground with regard to functional disorders of the foot and their causes. [ED. NOTE: This is an interesting and practical article, which will repay a careful perusal. It should be read in the original.] Creer<sup>609</sup> gives an interesting account of the treatment of disabling foot conditions in England, particularly in the light of the fact that the chiropodist is recognized there as an adjunct to the physician. [ED. NOTE: While such an arrangement is sound when it can be properly controlled, as

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607. Jones, R. L.: Human Foot: Experimental Study of Its Mechanics, and Role of Its Muscles and Ligaments in Support of Arch, *Am. J. Anat.* 68: 1-39 (Jan.) 1941.

608. Wiles, P.: Some Common Causes of Painful Feet, *Practitioner* 146: 389-394 (June) 1941.

609. Creer, W. S.: Foot Disabilities and Foot Clinics, *J. Roy. Inst. Pub. Health & Hyg.* 4:118-130 (May) 1941.



it apparently is in England, it is definitely questionable that it would work out in this country, where cults and isms so rapidly become important and so readily overstep the bounds of their capacity.] Creer properly emphasizes in his article the importance from an economic point of view of properly caring for disabling foot conditions.

*Hollow Foot.*—Huber<sup>610</sup> calls attention to the insufficiency of the hollow or high-arched foot in industrial workers and the possibility that trauma (of occupation) may cause hollow foot. [Ed. Note: One of us (R.L.D.) has long felt that the high-arched foot as a form of foot imbalance has been too generally neglected and suggests that this article is well worth the consideration of those interested in conditions affecting the foot. Some of the methods of treatment which Huber advises cannot be accepted unqualifiedly, e. g., tenotomy, for it is doubted that hollow foot can ever be corrected by such a procedure. Proper attention to the shoe is far more likely to give relief, and if operation is considered necessary, the operative procedure should be directed toward correcting the faulty alinement of the bones of the foot. Usually a midtarsal arthrodesis is necessary to accomplish this result.]

*Conditions Involving the Foot in Relation to Military Service.*—Helfet<sup>611</sup> recommends dividing into two groups the foot strain found in soldiers: (1) conditions affecting a flexible foot and (2) those affecting a rigid foot. He believes that distinguishing between the rigid and the flexible types of foot is definitely important. Treatment is based on the type of foot and correction to be secured by exercises, relief of pressure on bony points and satisfactory fitting of army shoes. Experience indicates that proper fitting of the shoe or the boot is the most important factor in maintaining foot efficiency in military service. Geckeler<sup>612</sup> thoroughly discusses the examination of the feet of selectees for military service and gives in detail the standards used in determining whether the selectee is to be accepted or rejected. The various types of conditions affecting the foot encountered in such examining work are discussed, and treatment is suggested. A similar article by Todd<sup>613</sup> contains a great deal of useful information on the examination and the care of the feet of those in the armed services. Practically all of the important points he makes and the methods of treatment

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610. Huber, H. H.: *Hollow Foot in Industry*, Wisconsin M. J. **40**:30 (Jan.) 1941.

611. Helfet, A. J.: *Treatment of Soldier's Foot*, J. Roy. Army M. Corps. **76**:282-285 (May) 1941.

612. Geckeler, E. O.: *Disorders of Foot in Relation to Military Service*, M. Clin. North America **25**:1843-1857 (Nov.) 1941.

613. Todd, A. H.: *Treatment of Flat Feet in Recruits*, M. Press **206**:130-136 (Aug. 13) 1941.

he advises are sound. It deals in a thorough way with the problems commonly encountered and gives many helpful suggestions. Both these articles should be of great interest and value to those who examine troops or who are in active service with troops. Kreglinger<sup>614</sup> ascribes the ability of the German troops to march 50 to 60 kilometers per day to the type of shoes they wear. This shoe is one with a thin sole, a broad toe and a long broad low heel. He claims that proper mobility of the foot is permitted in a shoe of this type, thus relieving strain.

*Hallux Valgus.*—Stracker<sup>615</sup> outlines the pathologic changes involved in hallux valgus and discusses the theories of its pathogenesis. He believes that the harmful effects of shoes are overemphasized and that the basic cause of the condition is a pathologic relation between the structure and the function of the foot. There may be other factors, such as polyarthrititis or synovial changes in the joint of the great toe. He considers that treatment may be conservative or operative in accordance with the symptoms and their causes. Conservative measures include proper fitting of shoes and stockings, the use of various types of bandages and splints for straightening the great toe and exercises tending to strengthen the adductor muscles. He recommends protecting the painful bunion by various protective covers and ointments. With regard to operative treatment he reviews the technic and the results of the more common operations and stresses the indications for each type of operation. He advises against osteotomy unless prolonged rest in bed is possible and recommends operations involving the soft tissues only (capsules, ligaments, and tendons). [Ed. NOTE: The various agents which Stracker has recommended for the correction of hallux valgus, such as bandages, splints and exercises, have in the experience of one of us (R.L.D.) met with practically no success in the correction of the condition. When hallux valgus or bunion is symptom producing, a properly planned operation will give a much more satisfactory result and relieve the patient of the constant necessity of applying bandages and protectors to the uncomfortable foot. It has not been the experience of this editor that operations on the soft parts alone are successful. Removal of the exostosis and correction of the valgus deformity are necessary for a successful outcome.] Veyrassat and Berner<sup>616</sup> report the results of a follow-up study of 19 patients operated on by Hütter's technic. Their observations do not

614. Kreglinger, G.: Footwear and Marching Capacity, *Med. Klin.* **36**: 1163-1164 (Oct. 18) 1940.

615. Stracker, O.: Hallux Valgus, *Wien. klin. Wchnschr.* **53**:885-889 (Nov.1) 1940.

616. Veyrassat, J., and Berner, A.: Hallux Valgus, Late Results of Hütter Operation, *Schweiz. med. Wchnschr.* **71**:587-590 (May 3) 1941.

justify the usual objections to this operation, namely, that it destroys the normal anterior point of support of the foot and creates postoperative flatfoot. In cases in which flatfoot was present, the authors attribute it to hallux valgus and not to the operation. They caution against too extensive resection of the head of the first metatarsal bone. Satisfactory results are obtained by resection of only 8 to 10 mm. They believe that a marked advantage of Hünter's operation as compared with other types is the rapidity of convalescence, most patients being able to resume normal activity within one month. [Ed. Note: Hünter's procedure does give satisfactory results, but it does carry a real possibility of destroying proper foot balance. The same result can be obtained by the Keller operation without the risk of later disturbance of foot balance.] Hansen<sup>617</sup> reports a follow-up study of patients with hallux valgus on whom Hünter, Mayo and Hohmann operations were performed. This series covers patients one to fifteen years after operation. It was found that 6 patients on whom the Hünter operation (resection of the head of the first metatarsal) was done had satisfactory position of the great toe in all cases, but the mobility in the joint was poor, 2 patients showing complete ankylosis. Hansen concludes that the Hünter operation is best suited for patients who before operation have articular changes and flatfoot. In 8 cases in which the Mayo operation was done there was improvement after operation, but in none was the result completely satisfactory, the mobility of the joints being bad in the majority of the cases. Hansen feels that the best results were obtained from the Hohmann operation. All 16 patients operated on walked with natural locomotion, while the mobility of the joint was limited in only 2 cases. Mayr<sup>618</sup> believes that most of the patients with severe hallux valgus rejected from military service may be restored to normal function by means of the Hohmann operation. This operation consists of a wedge-shaped osteotomy close to the head of the first metatarsal bone with simultaneous shortening of the bone from 1 to 2 cm. Mayr stresses the point that the proximal phalangeal joints of the large and small toes should be on the same level after operation. He believes that after osteotomy the metatarsal head should be pushed as far as possible in a lateral and plantar direction and that the abductor hallucis should be displaced laterally. He uses a plaster cast after the operation to correct the spread foot and requires four weeks' rest in bed. Mayr bases his con-

617. Hansen, N. S.: After-Examination of Patients with Hallux Valgus Operated on According to Hünter, Mayo and Hohmann Methods, *Nord. med. (Hospitalstid.)* 9:135-138 (Jan. 11) 1941.

618. Mayr, O.: Surgical Therapy of Hallux Valgus in Wartime, *Arch. f. orthop. u. Unfall-Chir.* 40:485-491, 1940.

clusions on 20 cases in civilian life in which he obtained excellent results from both a functional and a cosmetic point of view. He stresses the point that this operation is indicated only for young persons with no arthritic changes in the first metatarsophalangeal joint. [ED. NOTE: One of us (R.L.D.) unquestionably agrees with Mayr that this operation should be reserved for young patients without arthritis. This editor would go farther than this and state that when such changes are present this operation is definitely contraindicated.] Anderson<sup>619</sup> presents a series of cases of hallux valgus which he adds to a previous series reported from the orthopedic department of the Massachusetts General Hospital, Boston. The operation employed in this series was the Keller operation; it gave satisfactory results. [ED. NOTE: It should be appreciated that while the Keller operation is perhaps the most generally satisfactory type of operation for the correction of hallux valgus it does not correct the metatarsus varus primus which is so frequently an underlying cause of the condition; unless this metatarsus varus primus is corrected, a relapse or an unsatisfactory outcome may result. The Lapidus operation is the only described procedure which effectively overcomes metatarsus varus primus.] E. A. Jones<sup>620</sup> reports a series of cases of hallux valgus treated by the McBride operation and points out certain advantages of the operation. The chief advantages, he feels, are that the joint is not attacked, that there is no fracture made of the metatarsal head and that it is designed to prevent and correct muscle imbalance.

Batts<sup>621</sup> describes an ingenious method of holding the great toe in the corrected position after bunionectomy or the correction of hallux valgus. A rubber glove is cut out; the thumb portion and the thumb side of the wrist and the entirety of the wrist are used, the fingers being cut off. The wrist portion is then placed around the ankle and the thumb portion is placed around the distal end of the great toe. The elasticity of the rubber glove tends to hold the great toe in a varus position. [ED. NOTE: One of us (R.L.D.) has used this device and has found it satisfactory.]

*Hallux Varus.*—McElvenny<sup>622</sup> states that the condition of hallux varus is an unusual deformity and is usually unilateral. The first metatarsal bone is shorter and broader than normal and projects medially

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619. Anderson, R. L.: Hallux Valgus, West Virginia M. J. **37**:289-292 (July) 1941.

620. Jones, E. A.: McBride Operation for Hallux Valgus, Tr. New England S. Soc. **23**:57-60, 1941.

621. Batts, M., Jr.: Simple Corrective Device for Hallux Valgus, J. Bone & Joint Surg. **23**:183 (Jan.) 1941.

622. McElvenny, R. T.: Hallux Varus, Quart. Bull. Northwestern Univ. M. School **15**:277-280, 1941.

so that it lies in a line with the rear portion of the foot. The thickened first metatarsal bone may in some ways be considered a fusion of two metatarsal bones. The author describes an operation for the correction of hallux varus which is complicated; the description should be read in the original, since the accompanying illustrations are necessary to make the technic clear.

*Measurements of Foot Movements.*—Manter,<sup>623</sup> an anatomist, describes an ingenious apparatus for measuring movements in the subtalar and transverse tarsal joints. The article is largely technical and should be read in the original; the chief clinical interest lies in the evidence it provides to support elevation of the inner side of the heel and the outer margin of the forepart of the shoe for the correction of pronation. Thomsen<sup>624</sup> and Ott<sup>625</sup> describe the use of an apparatus designed by Thomsen for measuring the anterior part of the foot, its passive spreading when supporting weight and its active narrowing by muscular contraction. The subject discussed is only of academic interest and has little practical application in the treatment of conditions affecting the foot.

*Conditions Involving the Foot in Children.*—Boorstein<sup>626</sup> gives statistics on the prevalence of flatfoot in the newborn. He strongly urges a careful appraisal of foot structure in the newborn child and a careful search for abnormalities on the ground that much foot imbalance is attributable to mild abnormalities in structure present at birth. He urges early treatment by strapping and exercises. While careful inspection of the infant's foot should unquestionably be part of the complete examination that is given the newborn, and while any detectable abnormality demands corrective measures, the diagnosis of flatfoot in the newborn hardly seems possible, since true development of the arch of the foot does not begin until weight bearing is started. Sofield<sup>627</sup> has written a satisfactory article on foot hygiene for children with normal feet. Proper shoeing of the normal foot of a child and the importance of early correction by a qualified physician of all departures from normal are properly emphasized. [ED. NOTE: The article might well be read by all those whose practice has to do with the growing child.]

623. Manter, J. T.: Movements of Subtalar and Transverse Tarsal Joints, *Anat. Rec.* **80**:397-410 (Aug. 25) 1941.

624. Thomsen, W.: New Apparatus for Measurement of Passive and Active Changes in Breadth of Foot, *Ztschr. f. Orthop.* **71**:182-189, 1940.

625. Ott, L.: Passive and Active Variations in Anterior Part of Foot, *Arch. f. orthop. u. Unfall-Chir.* **40**:446-457, 1940.

626. Boorstein, S. W.: Flat Feet at Birth, *Hygeia* **19**:372-374 (May) 1941.

627. Sofield, H. A.: Care of Feet of Normal Children, *Illinois M. J.* **79**:253-256 (March) 1941.

*Exostosis on the Os Calcis.*—Frohlich<sup>628</sup> calls attention to the formation of an exostosis on the upper posterior pole of the os calcis (Haglund heel), which is often confused with achilles bursitis. Simple removal of the exostosis is all that is necessary for cure. Thomsen<sup>629</sup> discusses the same subject and arrives at the same conclusion, namely, that simple removal is all that is necessary. He has discontinued the complicated operative procedure advised by himself in the past.

*Accessory Bones of the Foot.*—In several articles on supernumerary bones of the foot, differences of opinion are expressed. Licht<sup>630</sup> and Delano<sup>631</sup> discuss bipartite os naviculare pedis and os intermetatarsium (a small accessory bone lying between the bases of the metatarsal bones) and come to the conclusion that such supernumerary bones are rarely of any clinical importance. Gottlieb<sup>632</sup> and Perez<sup>633</sup> believe that the accessory bones frequently cause irritation and inflammatory conditions and are of definite clinical importance. There can be no doubt that an accessory scaphoid bone because it interferes with the attachment of the tendon of the tibialis posticus muscle does allow pronation of the foot and that frequently irritation over the accessory scaphoid bone occurs because of pressure against the shoe. Careful shoeing of the foot and correction of pronation will relieve any irritation present, but the accompanying pronation or flatfoot can be completely corrected only by appropriate operative measures, such as Kidner's operation.

*Diseases and Injuries of the Tendo Achillis.*—Williams<sup>634</sup> reports 43 cases of tenosynovitis of the tendo achillis and emphasizes the diagnostic importance of pain in the heel and along the tendon. The author considers of diagnostic importance pain in the heel and along the Achilles tendon, swelling over the lower end of the tendon sheath and crepitus over the tendon on movement. These symptoms differentiate the condition from achilles bursitis, since in cases of the latter condi-

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628. Frohlich, E.: Abnormalities of the Calcaneum, the Haglund Heel, *Röntgenpraxis* 12:221-224 (June) 1940.

629. Thomsen, W.: Impracticability of Suggested Surgical Therapy of Haglund Heel, *Ztschr. f. Orthop.* 71:256-260, 1940.

630. Licht, E. deF.: Bipartite Os Naviculare Pedis, *Acta radiol.* 22:377-382, 1941.

631. Delano, P. J.: Os Intermetatarsium: Unusual Variant, *Radiology* 37:102-103 (July) 1941.

632. Gottlieb, A.: Clinical Significance of Accessory Bones of Foot, *West. J. Surg.* 49:452-453 (Aug.) 1941.

633. Perez, I. P.: Osteochondrosis of Supernumerary Scaphoid Bone: Cases, *Cir. ortop. y traumatol., Habana* 8:90-96 (July-Sept.) 1940.

634. Williams, A. A.: Tenosynovitis of Tendo Achillis, *Brit. M. J.* 2:377-378 (Sept. 13) 1941.

tion, the pain is localized over the insertion of the tendon, is not accompanied by crepitus and usually comes on after violent exertion. The most important causative factor of tenosynovitis of the achilles tendon, according to Williams, is wearing shoes or boots which constrict the forepart of the foot and raise a ridge at the back over the heel which causes pressure on the tendo achillis. Williams believes that boots and extended marching do not cause tenosynovitis; this is a point worthy of notice. He advocates the wearing of loose-fitting shoes and boots for those doing a great deal of marching and the treating of the condition once established by the injection of procaine hydrochloride into the sheath of the tendon. Davis<sup>635</sup> reports a number of cases of achilles bursitis coming on after prolonged marching. He has had success in treating this condition by using two cylinders of soft material 2 by 4 by 4 inches (5 by 10.2 by 10.2 cm.). A cylinder is placed on each side of the irritated area and strapped into place with adhesive tape.

Schnaberth<sup>636</sup> reports complete avulsion of the tendo achillis as a frequent accident in people over 30 years of age who take part in sports and who are unaccustomed to sport activities. He remarks on the wide retraction of the ends of the ruptured tendon, which he advocates suturing with silk rather than with fascia, after liberal resection of the splintered tendon fibers and cicatricial tissue if present. The after-treatment consists in holding the foot in the equinus position in plaster with the knee flexed. [ED. NOTE: One of us (R.L.D.) feels after a fairly wide experience that fascia lata is preferable to silk as a suture material, for while at times there may be considerable reaction following the use of fascia lata, the end results have been uniformly successful. When fascia is used, the foot does not have to be held in an equinus position; this obviates long and arduous physical therapy to correct, and motion may be instituted much earlier.] Silfverskiöld<sup>637</sup> reports 4 cases of acute and 3 of chronic subcutaneous rupture of the achilles tendon. In all cases he repairs the rupture by a flap 4 by 10 cm., from the posterior layer of the tendo achillis; this is turned down and rotated on the distal pedicle so that the smooth outer surface remains posterior. The flap is sutured along the side and to the attachment of the distal segment of the tendon. [ED. NOTE: Here again the use of fascia seems simpler and more effective, considering

635. Davis, H. R. L.: Ambulatory Treatment for Acute Retrocalcaneobursitis, *Canad. M. A. J.* **45**:77 (July) 1941.

636. Schnaberth, K.: Complete Avulsion of Achilles Tendon as Present Frequent Sports Injury: Surgical Therapy, *Arch. f. orthop. u. Unfall-Chir.* **40**:594-597, 1940.

637. Silfverskiöld, N.: Subcutaneous Total Rupture of Achilles Tendon and Its Treatment, *Acta chir. Scandinav.* **84**:393-413, 1941.

the shredding which occurs so frequently in the proximal part of the tendon from which a flap is taken.]

Marottoli<sup>638</sup> reviews previously reported cases and adds 2 new cases of ossification of the tendo achillis following injury. The ossification may be a single large center or two or more nuclei of varying sizes, usually independent of each other. The calcareous material is usually closely adherent to the tendon fibers and is excised with difficulty. The author recommends doing nothing unless the condition is causing symptoms, and then the ossification should be excised.

*Osteochondritis of the Ankle Joint.*—Mensor and Melody<sup>639</sup> point out that trauma to an ankle joint may result in breaking loose a fragment of joint cartilage which becomes a loose body. The size of such a loose body may be small enough to prevent its visualization in the ordinary roentgenogram. Taking a number of different exposures or using tomography to visualize such fragments is recommended if chronic pain and discomfort in an ankle following a sprain are complained of and do not respond to ordinary conservative treatment. One case is reported in which the result following operation was satisfactory. This is an interesting and practical observation.

Niederwieser and Grauer<sup>640</sup> believe that osteochondritis is not due to aseptic necrosis (osteochondritis dissecans) but to trauma, either to a single major injury or to repeated slight injuries. They report a case of osteochondritis of the ankle following reposition of a clubfoot in a child 3½ years old. They believe that spontaneous resorption of such loose bodies occurs frequently. [ED. NOTE: This has not been the experience of one of us (R.L.D.); removal is usually necessary.]

*Roentgen Studies of the Ankle Joint.*—Wolff<sup>641</sup> reports the result in a study of 26 ankles in which contrast mediums were used. He considers that arthrography gives valuable information concerning lesions about the ankle joint in that it shows abnormalities in the joints, the tendon sheaths and even the tibiofibular syndesmosis which are not visible in the ordinary roentgen examination. Hansson<sup>642</sup> also believes

638. Marottoli, O. R.: Ossification in Achilles Tendon Following Injury: Cases, *An. de cir.* 7:83-89 (March-June) 1941.

639. Menser, M. C., and Melody, G. F.: Osteochondritis Dissecans of Ankle Joint: Use of Tomography as Diagnostic Aid, *J. Bone & Joint Surg.* 23:903-909 (Oct.) 1941.

640. Niederwieser, V., and Grauer, J.: Loose Bodies in Ankle, Traumatic Osteochondrolysis, Unusual Localization in Ankle Following Redressement for Congenital Club Foot, Spontaneous Healing, *Röntgenpraxis* 12:152-156 (April) 1940.

641. Wolff, A.: Arthrography of Ankle Joint, *Nord. med.* (Norsk mag. i. lægevidensk.) 8:2449-2455 (Dec. 14) 1940.

642. Hansson, C. J.: Arthrographic Studies on Ankle Joint, *Acta radiol.* 22:281-287, 1941.



in the value of arthrography. He uses 3 to 6 cc. of 35 per cent solution of diodrast injected into the ankle joint after preliminary anesthesia has been induced with procaine hydrochloride. Hansson is particularly impressed with the information about the condition of the tibiofibular syndesmosis which can be obtained with this method.

Santora<sup>643</sup> gives a position for taking roentgenograms of the ankle joint which, according to the author, gives a much clearer view of the bones of the foot than the one ordinarily used. The patient is placed in a sitting position with the plantar surface of the foot resting on the film holder; this in turn is resting on a block angulated to 23 degrees, the heel being at the lower end and the toes at the upper end of the incline. The x-ray tube is tilted at 10 degrees and turned toward the ankle joint. According to Santora the central rays pass through the talotibial joint and demonstrate fractures of the tibia and the fibula which may be missed by the ordinary technic. The ankle joint is a complicated and important joint, and too much care cannot be exercised in getting adequate roentgenograms when injury to the joint is suspected.

The Moreaus<sup>644</sup> describe a method of roentgen examination for talipes varus and talipes valgus. The roentgenograms are taken with the patient standing facing a portable roentgen apparatus. The feet are perfectly parallel with their internal edges about 5 cm. apart. The centers of the heel and of the forepart of the foot are in line with the normal roentgen ray. The focus is fixed at a distance of 70 cm. and 12 cm. below the horizontal plane of the foot support. The roentgenogram shows the lower portion of the calcaneum, the tibiotarsal joint and the lower portions of the tibia and the os peroneum. Both feet appear in the same film. The authors have established landmarks by which to fix numerically the normal and pathologic angular views, thereby permitting recognition of deformity.

*March Fractures.*—Wilhelm<sup>645</sup> reports 3 cases of spontaneous fracture in soldiers in 2 of which the metatarsals were involved and in 1 on which the pelvis was affected. His theory is that such accidents are caused by the constant vibration set up during marching. He points out that the patients were of the asthenic constitutional type, unaccustomed to physical exertion. He advises physical training for all young

643. Santora, P. J.: Anteroposterior View of Ankle Joint and Foot, *Am. J. Roentgenol.* 45:127-128 (Jan.) 1941.

644. Moreau, J. E., and Moreau, M. H.: Talipes Valgus and Talipes Varus: A Roentgen Study, *Rev. argent. de reumatol.* 6:48-53 (May) 1941.

645. Wilhelm: "Gradual" Fractures (March Fractures): Based on Recent Observations on Soldiers, *Deutsche Ztschr. f. Chir.* 254:11-19, 1940.

men with special emphasis on exercises tending to strengthen the muscles and the ligaments of the foot and a diet rich in vitamins. Moore and Bracher<sup>646</sup> have observed march fractures in seasoned soldiers in good health and ascribe the fracture to unusual strain on a weak second, third or fourth metatarsal bone. Unequal distribution of weight on the metatarsal bones because of faulty foot balance seems to be the most logical explanation of march fracture.

*Injuries to the Foot and the Ankle.*—Childress<sup>647</sup> has written an impressive article on subfascial hemorrhage or hematoma complicating crushing injuries of the foot. The conclusions are interesting and are as follows: 1. Subfascial hemorrhage of the dorsum of the foot frequently complicates metatarsal fractures and soft tissue hemorrhage caused by crushing trauma. 2. The cruciate ligament of the foot may act as a constricting band in subfascial swelling; the condition was produced in 8 feet from cadavers into which dye solution was injected. 3. Immediate multiple incisions to release and remove subfascial hematoma is the treatment indicated in cases in which this is severe. 4. Release by transverse section of the cruciate ligament and the transverse ligament of the foot and the ankle should be considered in cases in which there are persistent circulatory blocks. 5. Delayed or inadequate treatment results in congealed foot or in the necrosis of the soft part of the dorsal part and the forepart of the foot and the toes. [Ed. NOTE: A similar condition has been noted in the hand by one of us (R.L.D.) following multiple fractures due to crushing violence.]

Gill and Abbott<sup>648</sup> call attention to the late results which follow fracture or separation of the medial malleolus in children. This injury may lead to premature cessation of growth in the medial portion of the distal epiphysal plate at the lower end of the tibia with resulting varus deformity of the foot and the ankle as time goes on. The authors advise careful immobilization in cases in which the condition is fresh, fusion of the distal tibial epiphysis in cases in which the condition is developing and correction of the deformity by low oblique osteotomy passing through the area of deformity or wedge osteotomy in old cases with established deformity. The possibility of interference with the distal epiphysis of the tibia with later bone deformity should be constantly borne in mind when dealing with such fractures in chil-

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646. Moore, P. F., and Bracher, A. N.: March Fracture: Report of Three Cases. *War Med.* 1:50-54 (Jan.) 1941.

647. Childress, H. M.: Subfascial Hematoma as Complication of Crushing Injuries to Foot, *J. Bone & Joint Surg.* 23:251-255 (April) 1941.

648. Gill, G. G., and Abbott, L. C.: Varus Deformity of Ankle Following Injury to Distal Epiphysal Cartilage of Tibia in Growing Children, *Surg., Gynec. & Obst.* 72:659-666 (March) 1941.

dren, and the parents should be informed at the outset of the possibility of later deformity developing for this reason.

Impink<sup>649</sup> discusses the importance of immediate reduction of all fractures of the tarsus and the metatarsus, since all of the bones of this region are weight bearing and failure to secure satisfactory position of fractures involving any of them may lead to serious disability. Impink prefers an unpadded plaster dressing for immobilization and the use of a walking iron incorporated in the plaster for all fractures except those of the os calcis; the weight bearing allowed by the walking iron is a stimulant to circulation. He advocates the application of an elastic bandage or an Unna's paste boot for swelling following the removal of the plaster. [ED. NOTE: While the use of an elastic bandage and the application of Unna's paste boot may be helpful when there is marked continuous swelling following the removal of plaster; as a rule, properly managed physical therapy rapidly brings about a return to normal, particularly if weight bearing has been permitted in plaster.]

*Subungual Glomus.*—Milch<sup>650</sup> makes the interesting observation that subungual glomus tumors cause a pressure atrophy on the dorsal surface of the terminal phalanx. This is due not to the pressure of the tumor itself but rather to the pulsation of the vascular portion of the tumor. Following removal of the tumor, the postoperative roentgenogram showed almost complete disappearance of the lacunas previously noted. In other words, the bone returned to normal. A series of cases is reported.

*Relaxation of the Tendo Achillis in Fracture of the Leg.*—Bustani<sup>651</sup> suggests relaxing the pull of the tendo achillis when setting fractures of the bones of the leg by infiltrating the muscles of the calf with a local anesthetic. He himself uses procaine hydrochloride. He states that he has had excellent results in a few cases. [ED. NOTE: This method of relaxing the tendo achillis has been used by Phelps for relaxing the contracted heel tendon in cases of spastic paralysis for diagnostic purposes, and it does give satisfactory relaxation. However, reduction of fractures of the bones of the leg requires general or intravenous anesthesia. Such anesthesia gives complete relaxation of the muscles of the calf, making unnecessary the additional local measures described by Bustani. If general or intravenous anesthesia is contraindicated or unobtainable, the method suggested by Bustani seems to have definite merit.]

649. Impink, R. R.: Fractures of Foot, S. Clin. North America 20:1815-1837 (Dec.) 1940.

650. Milch, H.: Pressure Atrophy of Terminal Phalanx Due to Subungual Glomus, Bull. Hosp. Joint Dis. 2:128-132 (July) 1941.

651. Bustani, M.: Anesthesia of Achilles Tendon in Fractures of the Leg, Publ. méd., São Paulo 12:41-46 (Jan.-Feb.) 1941.

## XVII. CONDITIONS INVOLVING THE SHOULDER, NECK AND JAW

*Lesions Due to Injury and Disease of Bursas and Tendons About the Shoulder Joint.*—In a fairly complete outline of diseases of the shoulder Steindler<sup>652</sup> divides them into: (1) lesions of the bursa; (2) injuries to tendons and muscles overlying the bursa, and (3) other lesions, e. g., tendon rupture and brachial neuritis, which simulate bursitis. Differential diagnosis and treatment are discussed. In a similar type of paper Wilson<sup>653</sup> analyzes 168 cases of painful shoulder; 89 of these were lesions of the subacromial bursa; 27, lesions of the shoulder joint; 16, lesions of the bones; 10, lesions of the acromioclavicular joint, and 5, lesions of the biceps tendon. He believes that periarticular adhesions account for more cases of painful shoulder than calcareous deposits.

Wood<sup>654</sup> lists various systemic diseases, particularly those which involve the lung, which can produce pain in the region of the shoulder. The differential diagnosis is not always easy, but usually local tenderness and muscle spasm are absent in these systemic diseases.

An extensive study of calcium deposits about the shoulder joint has been made by B. M. Bosworth.<sup>655</sup> Six thousand and sixty-one persons, mostly normal people, were studied by fluoroscopic examination. One hundred and sixty-five, or 2.7 per cent, had calcium deposits in sufficient amount to show by fluoroscope; 70 of these persons had pain and discomfort in the shoulder at some time. Illness and infection played no part in the formation or regression of deposits. Trauma alone did not cause deposits. Such deposits might form in two months but usually required a longer time. Small deposits often disappeared without symptoms, but larger ones always caused symptoms. Large deposits were best treated by incision. D. M. Bosworth<sup>656</sup> describes a method of radical exploration of the shoulder which is not new, viz., a division of the deltoid fibers close to their acromial attachment. Fusion of the shoulder joint is advised when there is complete avulsion of the tendinous cuff. The technic of fluoroscopy of the shoulder and the method of

652. Steindler, A.: *Lesions About the Shoulder Joint*, Northwest Med. **40**: 3-7 (Jan.) 1941.

653. Wilson, P. D.: *The Painful Shoulder*, Brit. M. J. **2**:1261-1265 (Dec. 30) 1939.

654. Wood, O. T.: *Clinical Significance and Differential Diagnosis of Shoulder Pain: Clinic of Eight Cases*, Internat. Clin. **1**:18-24 (March) 1941.

655. Bosworth, B. M.: *Calcium Deposits in Shoulder and Subacromial Bursitis: Survey of 12,122 Shoulders*, J. A. M. A. **116**:2477-2482 (May 31) 1941.

656. Bosworth, D. M.: *Supraspinatus Syndrome: Symptomatology, Pathology and Repair*, J. A. M. A. **117**:422-428 (Aug. 9) 1941.

taking small localized roentgenograms of the calcium deposit are further described by B. M. Bosworth.<sup>657</sup>

Cleaves<sup>658</sup> describes a new film holder for roentgen examination of the shoulder. The film is placed about a bakelite tube covered with lead foil,  $1\frac{7}{8}$  inches (4.8 cm.) in diameter. This is placed in a second tube 2 inches (5 cm.) in diameter. The tube is then placed as high as possible in the axilla. The x-ray tube is centered about the shoulder. Good views are obtained of the humeral head and the acromioclavicular joint.

A discussion of inflammation in all bursas and ganglions including those about the shoulder is given by Cherry and Ghormley.<sup>659</sup> Excision is advised for most of them. Stumpfegger<sup>660</sup> claims to obtain relief of disability of the subdeltoid bursa with a protein extract from various organs of the body (Clauden) injected repeatedly into the bursa. Wertheim and Rovenstine<sup>661</sup> believe that an analgesic block of the suprascapular nerve at the suprascapular notch is the procedure of choice to relieve pain about the shoulder. After the use of 5 cc. of 5 per cent intracaine ( $\beta$ -diethylaminoethyl-p-ethoxybenzoate hydrochloride) in oil analgesia persisted for several weeks. Physical therapy and other procedures could then be carried out without pain. [ED. NOTE: Injections about the suprascapular nerve lead to anesthesia chiefly about the posterior aspect of the shoulder, but the method is simple and sometimes effective.]

Sutro and Cohen<sup>662</sup> studied 34 patients with calcification in the tendons of the shoulder for vitamin deficiency. Eight patients were given tocopherol, but they showed no more rapid subsidence of symptoms than control patients. Dick, Hunt and Ferry<sup>663</sup> report giving 1 Gm. of ammonium chloride four times a day to patients with calcification of

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657. Bosworth, B. M.: Examination of Shoulder for Calcium Deposits: Technic of Fluoroscopy and Spot-Film Roentgenography, *J. Bone & Joint Surg.* **23**: 567-577 (July) 1941.

658. Cleaves, E. N.: New Film Holder for Roentgen Examination of Shoulder, *Am. J. Roentgenol.* **45**:288-290 (Feb.) 1941.

659. Cherry, J. H., and Ghormley, R. K.: Bursa and Ganglion, *Am. J. Surg.* **52**:319-330 (May) 1941.

660. Stumpfegger, L.: Obliteration Processes in Clauden Therapy of Chronic Synovial Bursitis, *Zentralbl. f. Chir.* **68**:779-782 (April 26) 1941.

661. Wertheim, H. M., and Rovenstine, E. A.: Suprascapular Nerve Block, *Anesthesiology* **2**:541-545 (Sept.) 1941.

662. Sutro, C. J., and Cohen, L. J.: Basis and Treatment of Calcification of Tendinocapsular Tissues, Especially Supraspinatus Tendon, *Arch. Surg.* **42**:1065-1071 (June) 1941.

663. Dick, G. F.; Hunt, L. W., and Ferry, J. L.: Calcification of Supraspinatus Tendon: New Treatment, *J. A. M. A.* **116**:1202-1205 (March 22) 1941.

the supraspinatus tendon. More rapid disappearance of the calcium deposit was observed.

*Roentgen Therapy.*—Roentgen therapy has been advocated for peritendinitis calcarea. Pinner and Staderman<sup>664</sup> treated 56 patients with calcification in tendons; in 52 of these the calcification was in the supraspinatus tendon. Seventy to 100 r was given over the shoulder area every other day until the symptoms subsided. Rarely were more than five treatments necessary. Marked clinical improvement was noted in all cases. Longer treatment was sometimes required in the chronic cases. There was usually rapid absorption of the calcium deposit. A comparison between diathermy and roentgen treatment is made by Solomon and Morton.<sup>665</sup> Twenty-five patients with periarthritis of the shoulder were treated with roentgen therapy. In each group 60 per cent were relieved of their symptoms.

Roentgen treatment is advocated for subacromial bursitis by Jones,<sup>666</sup> who reports the treatment of 14 patients with relief of symptoms in all of them. At each treatment 350 r was given. More than one treatment was required for most of these patients. [ED. NOTE: Relief of pain from subacromial bursitis usually follows roentgen treatment, but physical therapy and at times manipulation are required to regain full motion in the shoulder joint in the chronic cases.]

*Recurrent Dislocation of the Shoulder.*—Recurrent dislocation of the shoulder is discussed by Ahlberg.<sup>667</sup> He reports a procedure similar to that of Nicola. The long head of the biceps is cut in the intertubercular groove and sutured to the bone. The distal end is sutured to the bone below the tuberosity. Heger<sup>668</sup> reports the relieving of recurrent dislocation of the shoulder by injecting the patient's blood at five day intervals and keeping the arm in a sling. About 6 cc. of blood is injected into the articular capsule through the deltoid muscle. No case records are given.

*Conditions Resulting from Injuries About the Head of the Humerus.*  
—Lesions about the head of the humerus are not uncommon with dis-

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664. Pinner, W. E., and Staderman, A. H.: Peritendinitis Calcarea, with Particular Reference to Calcification in Supraspinatus Tendon, U. S. Nav. M. Bull. 39:521-532 (Oct.) 1941.

665. Solomon, W. M., and Morton, J. L.: Periarthritis of the Shoulder: Comparison of Results Obtained by Physical Therapy and by Roentgen Therapy, Arch. Phys. Therapy 22:607-610 (Oct.) 1941.

666. Jones, O. O.: X-Ray Treatment of Subacromial Bursitis, New Orleans M. & S. J. 93:363-366 (Jan.) 1941.

667. Ahlberg, A.: Therapy of Habitual Dislocation of the Shoulder, Acta chir. Scandinav. 84:557-565, 1941.

668. Heger, B.: Conservative Treatment of Habitual Luxation of the Shoulder, Wien. med. Wchnschr. 91:22-24 (Jan. 11) 1941.

location of the shoulder and in professional athletes. Hill and Sachs<sup>669</sup> report that a frequently unrecognized fracture in the posterolateral aspect of the humeral head occurs with dislocations. At this region a compression fracture can be demonstrated by roentgenograms which show this posterolateral portion of the humeral head. Lesions in the bicipital groove can be demonstrated by roentgenograms taken with the patient supine and with the arm adducted and supinated, state Sachs, Hill and Chuinard.<sup>670</sup> Occasionally there is an additional groove lateral to the original one. Bennett<sup>671</sup> describes hypoplasia of cartilage, the development of loose bodies in the elbow joints and osteoarthritic deposits about the posterior part of the shoulder joint in professional athletes, particularly baseball pitchers, due to injury sustained in pitching. He obtains relief of symptoms and fairly normal function by the removal of osteoarthritic deposits and loose bodies at the shoulder and elbow joints. While such procedures may relieve symptoms, they rarely make possible a continuance of pitching baseball.

*Muscle and Tendon Rupture.*—Muscular and tendinous ruptures may occur in the neck and the shoulder. Wuthrich<sup>672</sup> reports the rupture of the distal tendon of the biceps brachii muscle. The torn tendon was sutured to the radial tuberosity with silk. The patient was doing full work as a laborer six months later. Rupture of the long head of the biceps brachii is said to be rare by Long.<sup>673</sup> Such a rupture on both sides is reported in a 31 year old man. Operation led to little improvement in function. A rupture of the pectoralis major muscle is reported by Pulaski and Chandlee<sup>674</sup> in a 67 year old man who fell and caught hold of a railing. Suturing of the muscle to the chest wall led to full recovery. Wenger<sup>675</sup> reports a tear in the omohyoid muscle by rupture of its binding fascia. This produced a slight tumor in the neck, a pulmonary hernia. Suture of the fascia led to disappearance of the tumor.

669. Hill, H. A., and Sachs, M. D.: Grooved Defect of Humeral Head, Frequently Unrecognized Complications of Dislocations of Shoulder Joint, *Radiology* **35**:690-700 (Dec.) 1940.

670. Sachs, M. D.; Hill, H. A., and Chuinard, E. L.: Further Studies of Shoulder Joint with Special Reference to Bicipital Groove, *Radiology* **36**:731-735 (June) 1941.

671. Bennett, G. E.: Shoulder and Elbow Lesions of Professional Baseball Pitcher, *J. A. M. A.* **117**:510-514 (Aug. 16) 1941.

672. Wuthrich, A.: Subcutaneous Rupture of Terminal Tendon of Biceps Brachii, *Beitr. z. klin. Chir.* **171**:370-375, 1940.

673. Long, L. P.: Bilateral Independent Rupture of Long Head Division of Biceps Brachii, *Am. J. Surg.* **51**:684-688 (March) 1941.

674. Pulaski, E. J., and Chandlee, B. H.: Ruptures of Pectoralis Major Muscle, *Surgery* **10**:309-312 (Aug.) 1941.

675. Wenger, H. L.: Subclavicular Dislocation of Omohyoid Muscle by Rupture of Its Binding Fascia, *J. Bone & Joint Surg.* **23**:682-683 (July) 1941.

*Acromioclavicular and Coracoclavicular Conditions.*—A method of treatment of acute acromioclavicular dislocation is described by Hart.<sup>676</sup> He applies a plaster spica cast with the arm in 45 degrees abduction. Downward pressure is applied by straps and a pad on the acromion for six to eight weeks. After four weeks the upper half of the arm cast is removed, and exercises are given.

Two methods of operative repair of acromioclavicular dislocation are reported. Mumford,<sup>677</sup> while believing that most patients recover with conservative treatment, advises operation if symptoms persist. Absence of part of the clavicle does not lead to disability. To relieve the pain of acromioclavicular dislocation he removes the distal end of the clavicle. Four cases are reported with prompt relief of symptoms and return to work in three to four weeks. B. M. Bosworth<sup>678</sup> advises the suspension of the scapula from the clavicle for acromioclavicular separation. This is done by fixing the clavicle to the coracoid process with a single vitallium screw. No support is required postoperatively, but heavy work is not permitted for six weeks.

Abnormalities of the clavicle and its articulations have been reported occasionally. Nutter<sup>679</sup> reports 12 examples of coracoclavicular articulations in 1,000 patients; in 6 patients the articulation was present on both sides. Slocum<sup>680</sup> reports 1 case of bilateral coracoclavicular articulation without symptoms.

*Cervical Rib and the Scalenus Anticus Syndrome.*—Stammel<sup>681</sup> has observed a fracture of a cervical rib which occurred in an automobile accident. There were no special symptoms. Hadley<sup>682</sup> found cervical ribs in 1 per cent of autopsies. He believes that there is a hereditary tendency to this abnormality. Late symptoms come from weakening and depression of the shoulder girdle.

A new method of treatment of pain resulting from spasm of the scalenus anticus muscle is described by Kaplan.<sup>683</sup> He injects a solution

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676. Hart, V. L.: Treatment of Acute Acromioclavicular Dislocation, J. Bone & Joint Surg. **23**:175-176 (Jan.) 1941.

677. Mumford, E. B.: Acromioclavicular Dislocation: New Operative Treatment, J. Bone & Joint Surg. **23**:799-802 (Oct.) 1941.

678. Bosworth, B. M.: Acromioclavicular Separation: New Method of Repair, Surg., Gynec. & Obst. **73**:866-871 (Dec.) 1941.

679. Nutter, P. D.: Coracoclavicular Articulations, J. Bone & Joint Surg. **23**:177-179 (Jan.) 1941.

680. Slocum, D. B.: Coracoclavicular Joint, Northwest Med. **40**:16 (Jan.) 1941.

681. Stammel, C. A.: Bilateral Cervical Ribs: Report of Case with Fracture of Left, Am. J. Roentgenol. **45**:730 (May) 1941.

682. Hadley, H. G.: Cervical Ribs, J. Maine M. A. **32**:197-198 (Aug.) 1941.

683. Kaplan, L.: Relation of Scalenus Anticus Muscle to Pain in Shoulder: Diagnostic and Therapeutic Value of Procaine Infiltration, Arch. Surg. **42**:739-757 (April) 1941.



of procaine hydrochloride into the scalenus anticus muscle. Seventy-eight injections were given to 40 patients without any untoward effect. Most of the patients were completely relieved. Sometimes permanent relief resulted from a single injection.

Conservative treatment is advocated by Hansson<sup>684</sup> for the cervicobrachial syndrome. He finds that an analysis of cases shows that in 85 per cent operation is not performed. In all cases the condition is related to the superior outlet of the thorax. The structures which may increase tension on the vessels and nerve fibers are: (1) a high first rib; (2) a cervical rib; (3) a spastic scalenus muscle; (4) increased traction from within the thorax, and (5) increased traction by the scapula and the upper extremity. The author advocates rest and support with an airplane splint or a figure of eight bandage for the cases in which the condition is in an early stage. Exercises for maintaining the shoulder high and correcting posture are given. Head correction is delayed because holding the head erect may increase tension on the brachial plexus. Surgical correction is reserved for those who do not respond to this treatment.

*Cleidocranial Dysostosis.*—A case of cleidocranial dysostosis is reviewed by Tuggle and Mitton.<sup>685</sup> There was a defect in the midportion of the clavicle. Frequently no inconvenience or weakness results from the deformity. Complications are more frequently psychologic than physical.

*Conditions About the Scapula.*—Two cases of scapula alata are reported by Foley and Wolf.<sup>686</sup> These resulted from paralysis of the serratus magnus muscle. In one the paralysis of the serratus muscles followed an abdominal operation. In the other the condition was caused by infantile paralysis. They describe a spinal brace with pads over the scapula which improves function and makes the deformity inconspicuous.

Brunnstrom<sup>687</sup> has studied 17 cases of isolated paralysis of muscles about the scapula. This has given her an excellent opportunity for studying the isolated function of these muscles on the opposite side. She finds that isolated paralysis of the trapezius muscle did not interfere appreciably with elevation of the arm. Isolated paralysis of the serratus magnus muscle caused much disability; the arm could not be elevated above the horizontal position. The levator scapulae muscle can take

684. Hansson, K. G.: Cervicobrachial Syndrome, *Arch. Phys. Therapy* **22**: 662-666 (Nov.) 1941.

685. Tuggle, A., and Mitton, K. L.: Clavicular Dysostosis, *Am. J. Roentgenol.* **45**:728-729 (May) 1941.

686. Foley, W. E., and Wolf, J.: Scapula Alata, *J. Iowa M. Soc.* **31**:424-426 (Sept.) 1941.

687. Brunnstrom, S.: Muscle Testing Around Shoulder Girdle, *J. Bone & Joint Surg.* **23**:263-272 (April) 1941.

over the function of the upper trapezius muscle, and the serratus can take over the function of the lower trapezius.

*The Jaw.*—Kleinberg<sup>688</sup> reports a case of unilateral dislocation of the temporomandibular joint caused by the forceful extraction of a tooth. There was a history of repeated attacks of locking and stiffness for three months. The joint was exposed through a vertical incision anterior to the temporal artery, curving 45 degrees anteriorly above the joint line. At operation a degenerated cartilage was found, and there was a ridge of bone on the anterior margin of the joint. The removal of these led to free movement in the temporomandibular joint. There was complete recovery.

Extra-articular bony ankylosis of the temporomandibular joint is reported by Berger.<sup>689</sup> This occurred in a 4 year old Negro boy after multiple fractures of the facial bones from the kick of a horse. The removal of a mass of bone which joined the coronoid process to the mandible led to the return of movement.

Beckwith<sup>690</sup> has observed that disturbances in the balance of occlusion of the teeth cause changes in the temporomandibular joint. Symptoms of this may be centered about the ear or may travel along the sensory branches of the fifth nerve. Sheets<sup>691</sup> reports that abnormalities of the jaw can give rise to certain common complaints, e. g. temporary impairment of the hearing, buzz in the ear, pain and tenderness about the ear, dizziness and headache, particularly if the molar teeth are lacking. The condylar head might push on the meniscus rather than guide it. Treatment consisted in resting the joint. In severe cases wiring may be required.

#### VIII. CONDITIONS INVOLVING THE ELBOW, FOREARM, WRIST AND HAND

*Surgical Approaches to the Elbow Joint.*—The Kocher incision is praised by Bertola.<sup>692</sup> He modifies the skin incision by displacing it backward halfway between the epicondyle and the posterior midline through the olecranon process. He extends the incision from about 6 cm. above the olecranon process to 6 cm. below, curving it like an

688. Kleinberg, S.: Traumatic Internal Derangement of Temporomandibular Joint, *Am. J. Orthodontics (Oral Surg. Sect.)* **27**:328-332 (June) 1941.

689. Berger, A.: Intra-Articular Bony Ankylosis of Temporomandibular Joint, *Bull. Hosp. Joint Dis.* **2**:27-33 (Jan.) 1941.

690. Beckwith, J. H.: Observations Concerning Temporomandibular Joint, *Bull. Jackson Mem. Hosp.* **3**:74-78 (Jan.) 1941.

691. Sheets, C. E., Jr.: Temporomandibular Joint, *Mil. Surgeon* **88**:529-538 (May) 1941.

692. Bertola, V. J.: New Incision for Elbow, *Prensa méd. argent.* **28**:479-484 (Feb. 26) 1941.

extended S to end by crossing the posterior midline, much as in the Kocher incision. By displacing Kocher's skin incision a few millimeters posteriorly, the author hopes to protect the cutaneous nerves and to respect more fully Langer's lines of tension, thus avoiding painful scars. For the remainder of the exposure Kocher's technic is used. [ED. NOTE: Never having observed a painful scar after years of using the Kocher incision, one of us (W. P. B.) sees little reason for this new incision.]

Kaplan<sup>693</sup> emphasizes the importance of pronation and supination of the forearm during exposure of the radial head. He suggests having the patient in a prone position with the forearm pronated so that the little finger is up from the arm board. His incision is carried from  $1\frac{1}{2}$  inches (3.8 cm.) above the epicondyle and directly over the epicondylar ridge distally for about 2 inches (5 cm.) below the radio-humeral joint. It separates the brachioradialis and the two radial extensor muscles of the carpus laterally and the extensor digitorum communis muscle medially. The supinator muscle is identified in the depths. The writer demonstrates the greater vulnerability of the posterior branch of the radial nerve with the forearm in supination and warns against this position. [ED. NOTE: The prone position of the patient certainly simplifies exposure of the radial head and merits Leo Mayer's recommendation.]

*Avulsion of the Distal Biceps Brachii Tendon.*—Avulsion of the distal biceps brachii tendon is so rare that little has appeared in the literature concerning this injury. Dobbie<sup>694</sup> presents a new case of his own and 1 of Plummer's. In one the biceps tendon was split and sutured to the tendon of the brachialis muscle, and in the other it was passed blindly through its normal tunnel and sutured with fascia to the ulna. In addition to these the writer reports 49 additional cases uncovered by four hundred and ninety inquiries, to 72.6 per cent of which there were replies. The mechanism of repair in these cases varied from actual replacement of a tendon on the bicipital tuberosity, or looping of fascia around the radius, to suturing the tendon to the brachialis muscle, the brachioradialis muscle, the lacertus fibrosus or adjacent fascia. The predominant method of repair was suture with silk through drill holes in the bicipital tuberosity.

The diagnosis apparently presented no difficulty, although it was impossible to differentiate clinically between avulsion and actual rupture of the biceps tendon. The subject is summarized, and the results are tabulated. Twenty-four cases are added from the literature, making a

693. Kaplan, E. B.: Surgical Approach to Proximal End of Radius and Its Use in Fractures of Head and Neck of Radius, *J. Bone & Joint Surg.* **23**:86-92 (Jan.) 1941.

694. Dobbie, R. P.: Avulsion of Lower Biceps Brachii Tendon: Analysis of Fifty-One Previously Unreported Cases, *Am. J. Surg.* **51**:662-683 (March) 1941.

total of 75. From a review of all of these it seems that the results are equally satisfactory whether the tendon is attached to the radius or to the adjacent soft parts of the forearm. In connection with reattaching the tendon to the radius complications arose in 2 cases, and the writer warns against the use of the more complicated method. After Dobbie's article had been published, an additional case was reported independently by Sharpe.<sup>695</sup> He found the lacertus fibrosus torn and frayed and the tendon coiled on itself. After exposure of the radial neck, the tendon was sutured to the bone with chromic catgut through drill holes. The author describes the operation as tedious. A case which was unknown to Dobbie was simultaneously reported by Ringel<sup>696</sup> of Schmieden's clinic at Frankfurt on the Main, Germany. He obtained a good result by suturing the avulsed tendon to the lacertus fibrosus and the surrounding soft parts. He emphasizes the simplicity of the technic and the good end results. Ringel's bibliography duplicates five of Dobbie's references and furnishes nine additional ones.

An interesting case is reported by Wolfe<sup>697</sup> in which a traumatic partial rupture of the lower end of the muscles from the tendon made diagnosis difficult. Repair of the ruptured portion resulted in complete recovery.

[ED. NOTE: Dobbie's collected experiences and opinions establish the fact that the inclination of most surgeons on being suddenly confronted with an avulsed tendon is to replace it accurately. Certainly the easier operation is to be preferred, and the end results justify this procedure.]

*Roentgenography of the Wrist.*—More accurate roentgen studies of the carpal canal are urged by Hart and Gaynor.<sup>698</sup> A tangential view of the palmar surface of the wrist with the fingers and the hand dorsiflexed outlines the carpal canal with the pisiform bone and the hook of the hamate bone on one side and the tubercle of the navicular bone and the crest of the greater multangular bones on the other side. In a second article<sup>699</sup> he demonstrates the utility of this projection in revealing a fracture of the ridge or the tuberosity of the greater multangular bone and in visualizing the area in which the hook of the hamate bone bruised the ulnar nerve.

695. Sharpe, W. E., Jr.: Avulsion of Distal Tendon of Biceps Brachii, *Am. J. Surg.* **54**:733-736 (Dec.) 1941.

696. Ringel, W.: The Clinical Aspects and Therapy of Avulsion of the Lower Biceps Tendon, *Zentralbl. f. Chir.* **68**:871-875 (May 10) 1941.

697. Wolfe, H. R. I.: Traumatic Rupture of the Biceps Brachialis, *J. Roy. Nav. M. Serv.* **27**:290-292 (July) 1941.

698. Hart, V. L., and Gaynor, V.: Roentgenographic Study of Carpal Canal, *J. Bone & Joint Surg.* **23**:382-383 (April) 1941.

699. Hart, V. L.: Two Unusual Injuries of the Wrist, *J. Bone & Joint Surg.* **23**:948-949 (Oct.) 1941.

*Anatomy of the Wrist.*—MacConaill<sup>700</sup> finds that according to function the carpus must be divided into three units. These comprise the navicular bone, the lunate and triquetral bones together and the distal mass formed of the hamate, capitate and trapezoid bones together. This includes all of the bones between the forearm and the metacarpal bones, second to fourth inclusive. The navicular bone is separated from the other two groups because it moves with the distal row in the earlier stages of volar flexion and with the proximal row in the later stages. Conversely, it moves with the proximal row in the early stages of dorsiflexion and with the distal row in the later stages. In dorsiflexion of the hand the muscular forces pulling on the metacarpal bones transmit the force directly to the hamate, capitate and trapezoid bones. These three bones rotate about an axis which passes through the head of the capitate bone at the glenoid fossa of the navicular bone. The ligaments connecting the bones shorten and draw the bones tightly together, locking them with a screwlike motion which is best studied in a fresh dissection. In the second stage of dorsiflexion, the lunate and triquetral bones are screwed against the navicular bone and brought to rest tightly against it so that the writer likens the whole mechanism to a screw clamp with both rows of bones being screwed tightly against the navicular bone. The movement of the bones in radial and ulnar deviation of the hand is also traced. As a result of an extensive study of the anatomy of the bones of the wrist it is suggested that the usual manipulation of the wrist be reversed in the reduction of dislocation of the carpal semilunar bone. Volar flexion is shown to open the space and permit easy reduction. Dorsiflexion is used to close the space and lock the bone in position. The latter position is fixated in plaster. The method has been used successfully in 9 cases of fresh dislocation.

This anatomic observation may have bearing on midcarpal dislocation, such as the one described by Scott<sup>701</sup> in a British soldier. The semilunar bone and the proximal third of the fractured scaphoid bone maintained their normal relation to the radius. The remaining carpal bones were displaced, dorsally, radially and proximally.

Carter<sup>702</sup> calls attention to the occurrence of a bony tumor on the dorsum of the wrist associated with aching and rapid fatigue of the hand. Overgrowth of bone similar to a pair of osteophytes occurs on either side of the third metacarpal-capitate joint. Various theories of causation have been advanced. The writer considers the lesion to be

700. MacConaill, M. A.: The Mechanical Anatomy of the Carpus and Its Bearings on Some Surgical Problems, *J. Anat.* **75**:166-175 (Jan.) 1941.

701. Scott, L. G.: Unusual Dislocation of the Carpal Bones, *Brit. M. J.* **1**:855 (June 7) 1941.

702. Carter, R. M.: Carpal Boss: Commonly Overlooked Deformity of Carpus, *J. Bone & Joint Surg.* **23**:935-940 (Oct.) 1941.

of gradual development. Isolated trauma seems to play no part. In 2 cases in which operation was performed to remove the protruding bone, recurrence was prompt. In a personal communication to the author Lambert notes two recurrences after two operations in a similar case. Carter concludes that operation is of little value. The clinical entity is largely of medicolegal interest. [ED. NOTE: Carter has performed a real service in calling the attention of the orthopedic surgeons to this clinical entity which should apparently be left alone or treated conservatively.]

Ganglions of the wrist and the hand are treated by Lyle<sup>703</sup> with roentgen therapy. Six of 21 patients have been followed for five years. Examination and questionnaires have shown that 17, or 81 per cent, of the tumors disappeared. Fourteen, or 78 per cent, of the patients complaining of pain were relieved, and 9, or 82 per cent, of those complaining of weakness had a return of normal function. In general, 17 had good results; 1 was improved; 2 were not improved, and 1 was not heard from. From one to eight treatments were necessary. If after the first treatment the tumor disappeared in a month, the treatment was considered sufficient. When the tumor persisted,  $1\frac{1}{2}$  erythema dose of radiation was given each month until results were obtained. If more than five treatments were necessary, the interval between treatments was increased. A distance of 23 cm. was used with no filter. [ED. NOTE: Evaluation of end results must be extremely guarded when considering a lesion which frequently disappears spontaneously. The indication for treatment of a ganglion should be pain and weakness. The frequent relief of these symptoms with Lyle's treatment recommends it as sound.]

Lotsch<sup>704</sup> urges substitution of the term "arthroma" for the inaccurate designation "ganglion." After trying a great variety of forms of treatment, he has finally decided in favor of aspiration and injection of an iodine solution.

*Madelung's Deformity.*—A classical case of Madelung's deformity is reported by the Rochers.<sup>705</sup> For the treatment of this condition Hucherson<sup>706</sup> recommends the Darrach operation. An incision is made longitudinally on the ulnar aspect of the forearm, extending from the tip of the ulnar styloid proximally. It is carried down to the periosteum

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703. Lyle, F. M.: Radiation Treatment of Ganglia of Wrist and Hand, *J. Bone & Joint Surg.* **23**:162-163 (Jan.) 1941.

704. Lotsch, F.: Nature and Therapy of Tendon Sheath Ganglion: Suggested Change in Nomenclature to "Arthroma." *Med. Klin.* **36**:676-677 (June 21) 1940.

705. Rocher, H. L., and Rocher, C.: Madelung's Disease: New Case, *J. de m d. de Bordeaux* **117**:225-228 (April 20-27) 1940.

706. Hucherson, D. C.: Darrach Operation for Lower Radioulnar Derangement, *Am. J. Surg.* **53**:237-241 (Aug.) 1941.

between the flexor and extensor carpal tendons. Care must be taken to avoid the dorsal branch of the ulnar nerve. The periosteum is then reflected from the lower portion of the ulna, and the bone is cut across obliquely, leaving the proximal fragment with a sloping margin. The lower fragment is then turned out of the wound, and the attachment of the capsule is divided close to the articular cartilage. The ulnar styloid is then cut across at its base and left behind with its attached collateral ligament. The periosteum is closed. The attachment is strong enough to prevent abduction laxity.

Alexander and Johnson<sup>707</sup> record a case of Madelung's deformity in which in addition to the typical deformity, roentgen examination showed bilateral fusion of the semilunar and cuneiform bones.

In a case of trauma simulating Madelung's deformity, Marottoli and Broca<sup>708</sup> obtained a good result from excision of the triangular radiolunar fibrocartilage. They emphasize the simplicity of this procedure in contrast to plastic operations on this ligament or on the annular ligaments. [ED. NOTE: The recurrence of discussions of Madelung's deformity in the literature and the multiplicity of therapeutic suggestions indicate clearly that the problem is far from solved.]

*DeQuervain's Disease.*—In 40 cases of deQuervain's disease, Weissenbach and Francon<sup>709</sup> obtained cures in 35 with conservative treatment, for the most part with hydrotherapy. The writers recommend immobilization and administration of sedatives for three weeks. If the symptoms are not relieved, thermal treatment without massage is instituted. If the symptoms persist after two months, surgical intervention is indicated. Wilberg<sup>710</sup> has studied 23 cases in which operation was done and reports 8 in detail. In isolated cases there seems to be a definite relation between this lesion and trauma. To impute trauma the author requires a definite history of injury or operative findings clearly indicating scarring of the tendon. [ED. NOTE: The variable response to therapy of this condition as indicated by studies of end results is undoubtedly due to the variable causation. Infectious and traumatic causes are predominant. Both factors may be operating to produce the symptoms. In the face of infection conservative therapy

707. Alexander, H. H., and Johnson, G. H.: Dyschondroplasia of Distal Radial Epiphysis (Madelung Deformity), with Fusion of Semilunar and Triangular Cuneiform Bones, *Am. J. Surg.* **53**:349-351 (Aug.) 1941.

708. Marottoli, O. R., and Broca, M.: Fibrocartilaginous Lesions of Inferior Radiocubital Joint, *Dia méd.*, December 1940 (Ed. espec., no. 10), pp. 205-206.

709. Weissenbach, R. J., and Francon, F.: Chronic Stenosing Tenosynovitis (de Quervain's Disease): Symptoms, Diagnosis and Therapy, *Rev. argent. de reumatol.* **5**:299-305 (March) 1941.

710. Wilberg, G.: De Quervain's Tendovaginitis as Sequel to Injuries of the Hand, *Nord. med. (Hygiea)* **10**:1929-1933 (June 21) 1941.

should be stubbornly adhered to. When the cause is exclusively traumatic and cicatricial contractures are present, immediate operation is justified.]

*Anatomy of the Hand.*—From studies based on dissection, injection and section of 92 adult human hands, Grodinsky and Holyoke<sup>711</sup> would like to revise the conception and the nomenclature with regard to fascial spaces of the palm. They describe midpalmar, adductor, thenar and hypothenar palmar spaces as distinct entities. They bound these accurately. Injection into the midpalmar space of small amounts of gelatin filled only one or two compartments. Increasingly large quantities filled the entire midpalmar space and extended along the lumbrical muscles distally toward their insertion dorsally. Still larger volumes resulted in the rupture of the oblique septum with extension into the adductor space. This term is used instead of the thenar space of Kanavel. The writers describe thenar and hypothenar spaces which are of little importance clinically because infections within them remain localized and bear no important relations to other spaces or sheaths. The serous tendon sheaths and the fibrous sheaths also are described. The writers differ somewhat with the findings published by Anson and Ashley.<sup>711a</sup>

In an interesting study of 913 residents of the island of Formosa, Hikita, Kasiba and Hamasaki<sup>712</sup> have compared the lengths of the index and ring fingers. There seemed to be no sexual variation. On the average, the index finger was longer than the ring finger. The reverse was true of both hands in 12 per cent, of the right hand in 24 per cent and of the left hand in 6 per cent. [ED. NOTE: This is another illustration of the variation within normal limits.]

*Dupuytren's Contracture.*—Dupuytren's contracture has come up for discussion on all sides again during the past year. Meyerding and associates<sup>713</sup> offer an excellent summary of the subject. On the basis of microscopic study in 57 cases the lesion is explained as a chronic inflammatory process involving the skin, the subcutaneous tissue and the interstitial connective tissue as well as the palmar fascia. The authors warn against confusion with fibrosarcoma. They emphasize the surgical skill necessary for treatment and offer no gadgety solution to

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711. Grodinsky, M., and Holyoke, E. A.: Fasciae and Fascial Spaces of Palm, *Anat. Rec.* **79**:435-451 (April 25) 1941.

711a. Anson, B. J., and Ashley, F. L.: Midpalmar Compartment, Associated Spaces and Limiting Layers, *Anat. Rec.* **78**:389-407 (Nov. 25) 1940.

712. Hikita, K.; Kasiba, M., and Hamasaki, Y.: Relative Length of Fingers, *Taiwan Igakkai Zasshi* **40**:415 (Feb.) 1941.

713. Meyerding, H. W.; Black, J. R., and Broders, A. C.: Etiology and Pathology of Dupuytren's Contracture, *Surg., Gynec. & Obst.* **72**:582-590 (March) 1941.



the problem. Adams<sup>714</sup> also emphasizes the good results which may be obtained by painstaking, time-consuming, delicate operation and warns against longitudinal incisions. [ED. NOTE: Meticulous operation is certainly the answer to the problem of Dupuytren's contracture. Longitudinal connecting incisions, if kept at the ulnar border of the palm as described by Koch, have not caused contractures.] Couceiro<sup>715</sup> reports a single case. He is impressed with the element of neurotrophic change. [ED. NOTE: His eleven references are from South American journals only; six of these are found in the *Revue neurologique*. He should read the article by Meyerding and associates.] Stern<sup>716</sup> suggests a new operative technic. After preliminary exposure he divides the palmar fascia longitudinally on a grooved director. Multiple cuts are made over the tendon sheaths and over the vessels and the nerves. With this start the deep septums are dissected out. The author reports 1 case. Use of a tunnel graft to relieve skin contractures is suggested by Skinner.<sup>717</sup> [ED. NOTE: The literature on Dupuytren's contracture is now voluminous. If each new writer were to read a few of the good existing articles and then perfect a meticulous surgical technic, fewer aids in the treatment would be necessary. Badly contracted skin will frequently stretch after the fascia has been removed. One should not be in a hurry to sacrifice skin. There are still unknown factors in the causation. The hereditary element must not be overlooked.]

*Grease Gun Injuries of the Hand.*—Another case of oil penetration of tissue is reported by Hughes.<sup>718</sup> Accidental tripping of the compressor of a Diesel engine while the nozzle was in contact with the palm of a worker's hand injected 2 to 3 cm. of Diesel oil into the palm at the base of the middle and ring fingers. Intractable pain soon followed numbness. Gangrene of the fingers necessitated amputation. Several questions are raised which are well answered by Mason and Queen.<sup>719</sup> They report 2 cases. Both injuries were caused by grease guns. In the first case a primary incision was made soon after the injury at the site of entrance of the oil into the palm. Considerable

714. Adams, H. D.: Dupuytren's Contracture, *Lahey Clin. Bull.* 2:75-78 (Jan.) 1941.

715. Couceiro, A.: Dupuytren's Contracture: So-Called Retraction of Palmar Aponeurosis: Case, *Neurobiologia* 3:396-403 (Dec.) 1940.

716. Stern, E. L.: New Operative Procedure for Dupuytren's Contracture, *Am. J. Surg.* 54:711-715 (Dec.) 1941.

717. Skinner, H. L.: Operative Correction by Use of Tunnel Skin Graft for Dupuytren's Contracture, *Surgery* 10:313-317 (Aug.) 1941.

718. Hughes, J. E.: Penetration of Tissue by Diesel Oil Under Pressure, *J. A. M. A.* 116:2848-2849 (June 28) 1941.

719. Mason, M. L., and Queen, F. B.: Grease Gun Injuries to Hand: Pathology and Treatment of Injuries (Oleomas) Following Injection of Grease Under High Pressure, *Quart. Bull. Northwestern Univ. M. School* 15:122-132, 1941.

grease was expressed. The incision healed but reopened to discharge pus. Later the writers dissected out numerous encapsulated and infiltrating greasy tumors which extended down to the fibrous sheath of the flexor tendon of the index finger and to either side of the phalanx, where the mass surrounded the digital nerves and vessels. There were numerous smaller prolongations necessitating a "long and painstaking dissection." In the second case there was penetration of the left index finger with grease when a grease gun exploded. Grease could be squeezed from a dotlike puncture wound on the palmar surface on the distal phalanx. A month after the injury the finger tip became enlarged and was finally operated on six months later. The subcutaneous tissues of the anterior closed space were found to have been converted into a dense grayish mass resembling scar tissue and containing numerous grossly visible cystic areas filled with gray oily fluid. The overlying skin was adherent to the mass and apparently involved in the same process over one half of the area of the volar surface of the phalanx. The fibrous and cystic process extended throughout the whole of the subcutaneous tissues of the phalanx down to the periosteum and the fibrous tissues over the insertion of the flexor digitorum profundus tendon. The involvement of the skin was not so great in extent as that of the subcutaneous tissues. All diseased tissue was removed and a flap graft used.

The irritating effect of oil or paraffin in the tissues has been well known for many years. It is not surprising, therefore, that various industrial oils and greases, if introduced accidentally or intentionally, should also cause disturbance. In the case of injection under great pressure there is added to the irritative effect of the oil itself the great distention of the tissues with the likelihood of subsequent gangrene. This holds true particularly when closed spaces are involved, as, for example, when the fingers are affected. Late manifestations of extensive fibrosis and granulomatous lesions well beyond the area of original involvement are inevitable. It is therefore advisable to attempt removal of the oleoma even in those instances in which it is present as a symptomless nodule under the skin.

*Epithelial Cysts.*—Yachnin and Summerill<sup>720</sup> report an additional case of "traumatic" implantation of an epithelial cyst in the terminal phalanx of the right fourth finger following a crushing injury with avulsion of the nail. Two years later pain appeared at the tip of the finger. Roentgen examination revealed a circular area of destruction in the cortex of the terminal phalanx. At operation a white mass was removed which revealed on microscopic examination a thin wall formed by stratified squamous epithelium surrounding a nest of keratin debris

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720. Yachnin, S. C., and Summerill, F.: Traumatic Implantation of Epithelial Cyst in Phalanx, J. A. M. A. **116**:1215-1218 (March 22) 1941.

in the formation of which there was no parakeratosis. The stratum granulosum and the rete mucosum were thick. The basal layer did not accompany these except in one place, where only a minute fragment was attached. The cyst apparently is the result of traumatic implantation of epithelial cells and not of traumatic stimulation of growth of cells of congenital inclusion.

Becker<sup>721</sup> reports 2 similar cases of pavement epithelial cysts of the distal phalanges of fingers. In the first case an amputation of half of the distal phalanx was performed three weeks after the injury. At this time there was a fracture through a cyst. Microscopic examination showed cystic areas lined with pavement epithelium. It appeared that the epithelial tissue was forced into the bone. However, no direct connection between the skin and the bone could be determined. A diagnosis of traumatic epithelial cyst was made. In the second case the roentgen and the clinical appearance were somewhat similar, but the cyst was minute. There was a history of only minor finger injuries. In this case a small white kernel was shelled out of the bone. The tumor was preponderantly epithelial tissue, and a diagnosis of epithelial tumor with marked degeneration was made. It was less definitely from the skin than in the previous case. The writer cites 9 cases from the literature. He inclines to a theory of traumatic origin, even though there is no definite history of injury. It is known that comparatively minor trauma suffices to introduce epithelial cysts into the soft parts. It is suggested that the history is sometimes inadequate to disclose the trauma causing the origin of the cyst. The author urges preoperative recognition to avoid the necessity of partial amputation. [ED. NOTE: A long interval between injury and discovery does not prove traumatic origin, but a short interval (three weeks) does exclude it.]

*Tendon Injuries.*—The treatment of tendons in compound injuries of the hand is presented by Bunnell<sup>722</sup> in his usual simple but masterly fashion. Fine stainless steel wire is advocated instead of silk, which is the next best suture material for tendons. Various stitches are shown. A simple figure of eight stitch for primary suture of extensor tendons is used in connection with splinting. The deep loop unites the tendon ends and the superficial one the skin surfaces. The entire suture may be easily removed. It has no strength and depends on splinting for the relief of strain. A strong suture for interval repair buries the knot at a distance from the suture line. It has the disadvantage of leaving wire fragments in the tendon. These are less irritating physiologically than silk but may cause some mechanical difficulty. A double right angle

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721. Becker, F.: Pavement Epithelium of Bones of Fingers, *Chirurg* 12:275-279 (May 1) 1940.

722. Bunnell, S.: Treatment of Tendons in Compound Injuries, *J. Bone & Joint Surg.* 23:240-250 (April) 1941.

stitch may be used in cases in which there is no strain and in which infection is feared. It may be used in connection with a pull out wire.

To obtain his goal of complete absence of suture material, Bunnell has devised the withdrawable tendon suture.

After a tendon is sutured, only the end of the tendon attached to the muscle exerts a pull. Therefore, the suture is spliced securely in this end, and the two ends are passed some distance down through the center of the distal tendon and on out through the skin. By pulling upon these sutures from the outside and anchoring them securely, the proximal end can be drawn down until the tendon ends are held approximated. Only one tiny stitch of blood-vessel silk or hairlike wire is then necessary for exact approximation of the tendon ends.

For the later withdrawal of the stitch a pull-out wire is left in place which will draw the stitch out backwards by its loop whenever the two stitch wires are cut. Both ends of the pull-out wire, after being placed through the loop of the stitch in the proximal tendon end, are threaded on a needle and passed up through the sheath some distance and out through the skin. The play of the wires through the sheath will allow a little movement in the tendon without strain on the juncture.

Tension is relieved by flexing the joints. The stitch wires can be anchored to the outside of the limb by passing them through adhesive plaster applied to the skin and then fastening them through a button, by "split shot" or to a loop of adhesive plaster over the end of the finger, or by tying the wire ends through a perforation in the fingernail. If any resistance is encountered when withdrawing the stitch by the pull-out wire, tension may be applied by fastening a light rubber band to the wire. At the next dressing the stitch will be out. The bend of the pull-out wire, where it loops through the stitch, should be pinched sharp, so that it will not encircle tissue.

[ED. NOTE: The value of Bunnell's contribution needs no comment. The entire article should be read carefully as there is not a word wasted. The illustrations are excellent; only his motion picture is superior in graphic teaching qualities.]

An interesting suggestion with regard to flexor tendon injuries comes from Blum.<sup>723</sup> He holds that one of the important adverse factors responsible for the poor results associated with division of flexor tendons is tension at the site of repair. He suggests open division of the muscle at the junction of the distal and middle thirds of the muscle to release this pull. About half of the thickness of the muscle is divided. This serves not only to relieve tension but to supply an additional  $\frac{1}{2}$  inch (1.3 cm.) to the tendon in cases in which this is necessary. In cases in which there is no shortening of the tendon, the increased length permits satisfactory splinting with less flexion. The cut in the muscle heals readily during the healing of the tendon. Two cases are submitted in which the procedure has been tried with success.

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723. Blum, L.: Partial Myotomy in Treatment of Divided Flexor Tendons: Two Cases, *Ann. Surg.* **113**:460-463 (March) 1941.

Another ingenious suggestion comes from Bove.<sup>724</sup> In 4 cases he has transfixed divided flexor tendons in the fingers with fine wires like those of Kirschner. The wires are incorporated in plaster to prevent the tendon ends from retracting.

Fleischer-Hansen<sup>725</sup> reports on the end results in 261 cases in which there were three hundred and eighty-seven tendon injuries. There were 256 cases in which there were compound tendon lesions; 157 extensor tendons were affected as compared with 99 flexor tendons. With regard to function, the end results were good for 56 per cent and poor for 44 per cent of the lesions of the extensor tendons, while for the injuries of the flexor tendons only 31 per cent of the end results were good and 69 per cent were poor. The best results were obtained in the cases in which tendon suture was done on the back of the hand. In cases of injury to the flexor tendons suture of the flexor pollicis longus gave the best results. Simultaneous suture of several tendons to several fingers at once greatly lowered the percentage of good end results; in only 10 per cent of the cases in which this was done were good end results obtained.

The unsatisfactory results were blamed on certain anatomic and anatomicophysiologic factors, infection and deficient technic. It is recommended by the writer that all patients with injuries of the tendons be admitted to the hospital and not treated as outpatients.

Mouchet<sup>726</sup> records the late spontaneous rupture of the extensor pollicis longus tendon ten years after a Colles fracture. [ED. NOTE: This is certainly one of the longest intervals on record.]

*Phalangization.*—The method of Pieri of freeing and isolating the first metacarpal bone in cases in which the thumb is missing is again brought to attention. Almasanu<sup>727</sup> reports a case in which this treatment was successful. The operation was performed immediately after the accident which destroyed the thumb. The procedure is advocated in two articles from Russia. Rogova<sup>728</sup> reports a case in which there was loss of considerable of the last four metacarpal bones with preservation of the first. Function was apparently well restored.

724. Bove, C.: Suturing of Flexor Tendons of Hand (Transfixation), *M. Rec.* **153**:94 (Feb. 5) 1941.

725. Fleischer-Hansen, C. C.: Lesions of Tendons and Their Prognosis with Respect to Function, *Nord. med. (Hospitalstid.)* **9**:88-98 (Jan. 11) 1941.

726. Mouchet, A.: Late Rupture of Extensor Pollicis Longus Tendon Ten Years After Fracture of Lower End of Radius: Case, *Presse méd.* **48**:1007-1008 (Dec. 11-14) 1940.

727. Almasanu, S.: Phalangization of First Metacarpal Bone: Case, *Rev. de chir., Bucuresti* **43**:807-809 (Nov.-Dec.) 1940.

728. Rogova, K. F.: Phalangization of First Metacarpal Bone, *Khirurgiya* **11**:150-151, 1939.

Shirokov <sup>729</sup> summarizes briefly the literature on operative replacement of the thumb. It is his opinion that Albrecht's operation is the best to date. This includes resection of the first dorsal interosseous muscle and transplantation of the insertion of the adductor pollicis muscle proximally. After anatomic studies and one preliminary operation, he obtained a good result in 1 case in which he added to Albrecht's technic by extirpating all of the adductor pollicis muscle except for the bundles of the oblique head which arise at the base of the second metacarpal bone, on the capitate bone and on the radial portion of the volar ligament. He conserved the point of attachment on the ulnar sesamoid bone. With this he combined resection of the medial portion of the abductor pollicis brevis muscle, the opponens pollicis muscle and the superficial head of the flexor brevis muscle. If the flexor pollicis longus muscle is not already adherent to a stump of the basal phalanx, it should be transplanted to the distal end of the metacarpal bone. For this method the writer claims greater range of motion for the first metacarpal bone, greater power and better cosmetic effect.

[ED. NOTE: Although the cosmetic effect of this operation is obviously inferior to that of the more complicated plastic procedures, the present international conflict will give rise to hand stumps which may be well handled by this method.]

*Traumatic Edema.*—Schörcher <sup>730</sup> emphasizes the reflex effect on the lymph vessels as well as on the blood vessels of traumatic edema of the hand. One case is reported in which six operations on the sympathetic nervous system failed. Improvement occurred after the introduction of silk suture drainage in the subcutaneous tissues from the hand to the middle of the forearm. With this procedure the edema disappeared within fourteen days.

#### XIX. AMPUTATIONS, APPARATUS AND TECHNIC

*Amputations.*—During the year of 1941 there has been a great deal of new literature pertaining to amputations and prostheses. The most important group of papers constitute chapters in a book to be published by the Council on Physical Therapy of the American Medical Association written by particularly well qualified surgeons and a carefully chosen group of artificial limb makers. Three of these papers were mentioned in last year's article on "Progress in Orthopedic Surgery." <sup>731</sup>

729. Shirokov, B. A.: Phalangization of First Metacarpal Bone in Plastic Restoration of Thumb: Anatomic Basis of Author's Method, *Khirurgiya* **11**:115-122, 1939.

730. Schörcher: Traumatic Edema of the Hand, *Beitr. z. klin. Chir.* **171**:176-194, 1940.

731. Progress in Orthopedic Surgery for 1940, *Arch. Surg.* **43**:866-932 (Nov.) 1941.

Gallie,<sup>732</sup> writing from experience based on 2,448 amputations of the lower extremity with the Canadian Army and Pension Board, which has functioned since the first World War, extols the end-bearing stumps such as result from a Gritti-Stokes or Symes amputation, which are not recommended by the British Ministry of Pensions. It is apparent that whereas these two amputations performed by the experienced amputator most often give good results they do not give uniformly good results when performed in a large organization, such as the British Ministry of Pensions, in which many different and inexperienced surgeons do the actual operating. A good deal also depends on the artificial limb maker's cooperation in the proper fitting of the limb for the best functioning of the stump.

Carnes<sup>733</sup> also advocates the end-bearing stump.

[ED. NOTE: Others with less experience should not be criticized for performing the simpler operations which are attended more often by success but which admittedly do not have the desirable end-bearing possibility.]

A modification of the Callander operation is described by Pearl.<sup>734</sup> He thinks it is desirable because his results were far more satisfactory than with the use of the orthodox technic. [ED. NOTE: In recent personal communications to one of us (J. W. W.), one from a member of the group of Consultants on Artificial Limbs of the Council on Physical Therapy of the American Medical Association and another from an experienced member of the Canadian Army and Pension Board, the opinion is expressed that the more complicated technic in this operation does not justify itself when end results are compared with the classical long anterior-short posterior flap operation done under a tourniquet.]

Maxeiner<sup>735</sup> urges the employment of what he calls a temporary tourniquet amputation in cases of extreme shock in which grave doubt exists relative to the patient's surviving the amputation of a hopelessly mutilated extremity. He employs several loops of "gum rubber tubing about the extremity at the lowest possible point at which the member must be sacrificed." Infection and putrefaction of the damaged extremity are controlled by wrapping the part below the tourniquet in a 10 per

732. Gallie, W. E.: The Experience of the Canadian Army and Pensions Board with Amputations of the Lower Extremity, *Ann. Surg.* **113**:925-931 (June) 1941.

733. Carnes, E. H.: Amputations, Stumps and Prostheses, *War Med.* **1**: 656-663 (Sept.) 1941.

734. Pearl, F. L.: Atraumatic Amputation Through the Lower Thigh (Callander): Modified Technic, *Surg., Gynec. & Obst.* **73**:381-387 (Sept.) 1941.

735. Maxeiner, S. R.: The Temporary Tourniquet Amputation, *Minnesota Med.* **24**:491-492 (June) 1941.

cent formaldehyde dressing encased in rubber sheeting. [ED. NOTE: One of us (J. W. W.) sees no reason why the usual Esmarch rubber bandage which is ordinarily used in work on an extremity could not be employed. The only difference is the constricting of a small circumferential area rather than larger areas constricted by the wider band ordinarily employed. It is suggested that in addition to this dressing another wide rubber bandage be employed over the rubber sheeting to insure the doing away with the disagreeably pungent odor.] Assurance is given that the initial pain is overcome by morphine or other sedatives and that this subsides in a few hours anyhow and that recovery from shock is surprisingly rapid. The time for the actual amputation may be elected, and the surgeon "may quite well wait a week." It will ordinarily be found that the tourniquet has cut its way through all of the soft tissue and that practically only the bone needs to be severed to obtain a satisfactory guillotine amputation.

The employment of refrigeration is advocated in a most important article by Allen<sup>736</sup> reporting opinions, experiences and technic from a large vascular disturbance clinic. After an extremity is thoroughly chilled to 5 C., it is found that amputations can be done painlessly and without shock. After chilling of the extremity with an ice bag technic described in detail, the amputation can be done unhurriedly at a point conveniently below the proximal level of chilling. A thorough discussion of the value of cold as a therapeutic agent, particularly, of course, with regard to diabetic and arteriosclerotic vascular disturbances, is given. The more assured survival of distal portions of extremities in which the vascular supply has been seriously diminished is claimed by the use of cold. The absence of heat diminishes the metabolic requirement to the amount of metabolism available and reacts more kindly than heat on the part affected. The use of cold in promoting healing in many other situations is discussed in a most convincing manner; this makes the article one that should be read carefully and thoughtfully in the original by all surgeons, particularly those operating on extremities. [ED. NOTE: The value of heat as a therapeutic agent has long been stressed, and it is just as important to understand the significance and value of the other extreme of temperature.]

McElvenny<sup>737</sup> reports a case of trauma in which the principles of refrigeration as stated by Allen were employed most successfully prior to the amputation of both legs.

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736. Allen, F. M.: Reduced Temperatures in Surgery: Surgery of Limbs, *Am. J. Surg.* 52:225-237 (May) 1941.

737. McElvenny, R. T.: The Effect of Cooling Traumatized and Potentially Infected Limbs, *Surg., Gynec. & Obst.* 73:263-264 (Aug.) 1941.



A German article by Angerer<sup>738</sup> reporting the satisfactory functional results following amputations of the toes and even the metatarsal heads necessitated by exposure to cold is reviewed. This suggests that there may be an overemphasis on the amount of disability to be expected from such operations.

A Spanish surgeon, Cotta dos Santos,<sup>739</sup> calls attention to the value of astragalectomy for the equinus deformities following Chopart's amputations (he calls it equinismus). [ED. NOTE: It is believed by one of us (J. W. W.) that if astragalectomy is to be considered as a retouching secondary procedure, this is a valuable article to emphasize the unsatisfactory results ordinarily to be expected from amputations of the fore-foot.]

An excellent brief history of amputations from the time of Hippocrates to the first World War is given by Carnes,<sup>740</sup> who discusses at length various important points already adequately stressed but all worth while reviewing. This is the only article in which cinematic amputations are mentioned, but they are spoken of rather unenthusiastically. It is stated that the results are not much better than with conventional methods. [ED. NOTE: It is obvious that the technicalities of this operation confine its employment to the ultraspecialized surgeon and certainly do not permit it to be done by the occasional amputator.]

In the chapter on reasons for reamputations and secondary operations in the report of the Council on Physical Therapy of the American Medical Association on amputations,<sup>740</sup> the principal cause is given as too much length. Others of less importance are: sloughing or ulceration, over the end of the stump, osteomyelitis or aseptic necrosis of the end of the bone, neuroma and finally neurosis. It was found that true malingering as a reason for reamputation is rare.

In another chapter<sup>741</sup> it is pointed out that surgeons frequently are too loath to amputate and that not enough regard is paid the patient's desires in this matter.

Brittain,<sup>742</sup> an English surgeon, calls attention to the advantage of performing some amputations in bed on seriously ill patients in order to facilitate the carrying out of intravenous procedures. [ED. NOTE:

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738. Angerer, H.: Physical Efficiency of Mountaineers After Loss of Lower Extremities, *Zentralbl. f. Chir.* **67**:2250-2251 (Nov. 30) 1940.

739. Cotta dos Santos, H.: Value of Ricard Amputation Operation in Crushing of Foot with Surgical Technic, *Rev. méd. munic.* **1**:226-235 (Feb.) 1941.

740. Reamputations and Secondary Operations, Council on Physical Therapy, J. A. M. A. **116**:2501 (May 31) 1941.

741. Physical Therapy in Amputations, Council on Physical Therapy, J. A. M. A. **116**:1519-1523 (April 5) 1941.

742. Brittain, H. A.: Amputation in Bed, *Brit. M. J.* **1**:192-193 (Feb. 8) 1941.

This is a reasonable common sense article which calls attention to a point possibly not frequently enough considered. There is nothing particularly unusual about the technic suggested except possibly its urging a thorough rehearsal before performing the amputation.]

Mohs, Sevringhaus and Schmidt<sup>743</sup> have collaborated in an article advocating conservative amputations of gangrenous parts by fixing them with a twenty-four hour exposure to a zinc chloride paste; after this, if separation of fixed tissue has occurred, amputation is done with a scalpel and a bone rongeur. This sometimes takes several days. It is claimed that by this method freshly cut surfaces are avoided and the spread of infection is discouraged.

Willis and Teitelman<sup>744</sup> describe an interesting amputation technic in which after the shaping of an anterior flap a flat band retractor is passed posterior to the femoral shaft at the point of planned amputation and the posterior flap is fashioned in an unhurried manner, pressure being exerted on the uncut tissues against an underlying sterilized cork block. The retractor itself serves as a most satisfactory protector of the underlying tissues when the bone is sawed. The vessels and the nerves are easily identified and taken care of. [ED. NOTE: The chief but questionable advantage of this technic is the avoidance of a tourniquet, but it is feared that there would be a temptation to leave too long a posterior flap.]

In 1941 two articles on interscapulothoracic amputation, and one on interinnominoabdominal amputation appeared. No particularly new points have been brought out, but in Strode and Fennel's<sup>745</sup> article the most frequent indication for such a heroic surgical procedure is given as the presence of a relatively benign radioresistant tumor that cannot be widely enough excised locally, in other words a tumor that is locally malignant owing to its anatomic location and not to its morphologic composition. The authors report 2 cases in which interscapulothoracic amputation was done. One was a case of metastatic carcinoma, and the other, of primary sarcoma. The patients have survived, one fifteen years and the other two years. Montant and Perrier<sup>746</sup> report a patient with metastasis of hypernephroma to the right humerus who had an inter-

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743. Mohs, F. E.; Sevringhaus, E. L., and Schmidt, E. R.: Conservative Amputation of Gangrenous Parts by Chemosurgery, *Ann. Surg.* **114**:274-282 (Aug.) 1941.

744. Willis, D. A., and Teitelman, S. L.: Simplified Technic for Amputation Through Thigh, *Surgery* **10**:633-635 (Oct.) 1941.

745. Strode, J. E., and Fennel, E. A.: Treatment of Tumors of Shoulder Region by Interscapulothoracic Amputation, *Surgery* **9**:394-402 (March) 1941.

746. Montant, R., and Perrier, C.: Interscapulothoracic Disarticulation for Metastasis of Hypernephroma to Right Humerus: Secondary Nephrectomy, *Rev. méd. de la Suisse Rom.* **61**:170-175 (March 25) 1941.

scapulothoracic amputation performed and later survived a nephrectomy by which the tumor was identified. It is admitted that had this tumor been recognized before operation, the extensive amputation operation would not have been performed. Selig<sup>747</sup> gives the history of a patient on whom an interinnominoabdominal amputation was done for a Ewing tumor near the trochanter; the patient lived forty-five days after operation.

*Artificial Limbs.*—Five articles on artificial limbs describe such specialized points as the character of sockets, a pneumatic knee joint control arrangement admittedly noisy and lightness in weight. The Council on Physical Therapy of the American Medical Association<sup>748</sup> has a most excellent article discussing the industry itself, materials and construction. A new knee joint lock is mentioned which locks in extension when weight is borne on the heel and unlocks when weight is borne on the toe.

*Braces.*—As a by-product of the postoperative treatment of cup arthroplasties of the hip, Tobin<sup>749</sup> has assembled an anterior ring Thomas splint, with a Pearson attachment, which permits a good range of motion of both hip and knee while traction is being maintained.

*Apparatus.*—Two goniometers have been described. The one described by Cooper<sup>750</sup> incorporates a fixed horizontal limb, employing a level which facilitates the measuring of joint angles from the horizontal position. The one described by Molander<sup>751</sup> includes the use of charts on which ranges of motion are recorded for the various joints, rubber stamps being employed to represent the different parts. Both are of value in cases in which more detailed records than usual are needed.

Krusen<sup>752</sup> has devised a custom-built heating cup for applying uniform heat to the shoulder. This consists of a covering made of electrical conducting material similar to that employed in heating deep sea diving suits. The axillary space is covered as well as all other areas of the shoulder.

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747. Selig, S.: Interinnomino-Abdominal (Hindquarter) Amputation, *J. Bone & Joint Surg.* **23**:929-934 (Oct.) 1941.

748. Manufacture of Artificial Limbs, Council on Physical Therapy, *J. A. M. A.* **117**:1441-1445 (Oct. 25) 1941.

749. Tobin, W. J.: Splint to Increase Hip and Knee Motion, *J. Bone & Joint Surg.* **23**:712-713, (July) 1941.

750. Cooper, W.: Simplified Arthrometer, *Ann. Surg.* **114**:316-317 (Aug.) 1941.

751. Molander, C. O., and Weinmann, B.: New Chart System for Recording Joint Measurements, *Physiotherapy Rev.* **21**:88-90 (March-April) 1941.

752. Krusen, F. H.: New Conductive Heating Device to Provide Uniform Heating of Periarticular Structures of Shoulder Joint, *Proc. Staff Meet., Mayo Clin.* **16**:328-329 (May 21) 1941.

Schneider<sup>753</sup> describes an adjustable osteoclast which permits pressure to be applied with great accuracy and a minimum of trauma and which is arranged so that it can be radiographically controlled. The apparatus is complicated, and the interested reader is referred to the original article for further detailed information and illustrations.

A crutch of simple design which extends only to the elbow and obviates the possibility of crutch paralysis is described by zur Verth.<sup>754</sup> This idea is not new, but it is believed that if information on this type of crutch were more generally available, its use would be more widespread.

*Surgical Instruments.*—Lyon, Cochran and Smith<sup>755</sup> have written an article which should be read in the original by those using bone screws. Important experimental work is reported to substantiate the recommendations regarding the selection of the proper type of screw. Original determinations to ascertain the proper drill size for the screws tested are presented. The importance of using a screw with a coarse thread rather than one with a machine thread is emphasized. The tapering character of the usual wood screw is deprecated. [ED. NOTE: This is a most excellent article.]

The new, justly popular Luck electric bone saw and drill is described by its designer in an excellently written article.<sup>756</sup> Its various advantages, such as complete, easy sterilizability, light weight, key chuck and twin speed, are mentioned. [ED. NOTE: One of us (J. W. W.) has used this bone saw constantly for many months and finds that its claims are not overstated and that it can certainly be recommended.]

For the purpose of obtaining osteoperiosteal grafts of uniform thickness from the face of the tibia, Burns<sup>757</sup> has designed a chisel with a guard; this causes it to function as a plane and prevents the removal of more than a thickness of 3/16 inch (0.48 cm.) of the cortex. [ED. NOTE: One of us (J. W. W.) used this type of instrument several years ago and finally gave it up because most tibias are too hard and the cutting edge of the chisel would not continue to bite evenly but would jump out frequently.]

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753. Schneider, J.: Universal Osteoclast for Medical and Terminal Osteoclastis and Correction, *Arch. f. orthop. u. Unfall-Chir.* **40**:492-494, 1940.

754. zur Verth, M.: A New Type of Crutch, *Jahresk. f. ärztl. Fortbild.* **31**:16-17 (Dec.) 1940.

755. Lyon, W. F.; Cochran, J. R., and Smith, L.: Actual Holding Power of Various Screws in Bone, *Ann. Surg.* **114**:376-384 (Sept.) 1941.

756. Luck, J. V.: Electric Bone Saw and Drill, *Am. J. Surg.* **54**:505-507, (Nov.) 1941.

757. Burns, R. E.: Osteoperiosteal Chisel, *J. Bone & Joint Surg.* **23**:384-385 (April) 1941.

*Plaster Cast Technic.*—Many new publications on plaster cast technic have appeared. The most important is an English article by Creer,<sup>758</sup> who discusses in detail the making of a standard pattern of plaster-incorporated crinoline to assist in the rapid application of spica casts to the hip. Three different sections of the spica cast, namely, a posterior body piece, an anterior body piece and a leg piece, are made, each being seven or eight layers thick and of a size to fit the particular patient. When applied, there is ample overlap, and the entire cast is fixed with a few plaster bandages. Although this idea is not new, more detail is given in this article than usual, and its use should cut several minutes off the time employed for the application of a spica cast after an operation. [ED. NOTE: A thorough study of the original article is recommended.]

Sullivan<sup>759</sup> emphasizes once more the value of extensive cast immobilization in the treatment of wounds in the extremities, calling attention to the success of the Orr-Trueta method in cases in which this is the prime factor.

It is feared that except on board ship or in a clinic closely associated with a machine shop the admittedly advantageous knee action shock-absorbing walking iron for a plaster cast devised by a machinist's mate in the United States Navy, Ferrell,<sup>760</sup> would be seldom manufactured. The ordinary rubber-covered metal stirrup, while not as comfortable, takes less room than the deluxe one pictured in the original article. The apparatus consists of two springy weight-bearing surfaces attached to the bottom of a cast.

*Internal Fixation.*—Six worth while papers discussing the use of metals in the internal fixation of bone show that the issue is still a live one, but it looks as though vitallium products are gradually being supplanted by the less expensive, tougher and more generally usable stainless steel products.

Key<sup>761</sup> calls attention to the value of the 18-8 S-MO stainless steel, which appears after extensive tests to be as nonirritating as vitallium, and recommends that articles made from it be standardized by the Fracture Committee of the American College of Surgeons and be properly marked for the protection of the surgeon.

758. Creer, W. S.: Standard Pattern for Hip Spica, *Lancet* 1:9-10 (Jan. 4) 1941.

759. Sullivan, J. E.: Immobilization in Treatment of Wounds of Extremities, *S. Clin. North America* 21:571-576 (April) 1941.

760. Ferrell, B. E.: Walking Appliance for Plaster Casts, *U. S. Nav. M. Bull.* 39:413-415 (July) 1941.

761. Key, J. A.: Stainless Steel and Vitallium in Internal Fixation of Bone: Comparison, *Arch. Surg.* 43:615-626 (Oct.) 1941.

Campbell, Meirowsky and Hyde<sup>762</sup> report on the toxicity of various alloys and metals, including ticonium (an alloy made up of nickel, cobalt, chromium and molybdenum, with a small amount of beryllium if it is to be cast), on fibroblast cultures. They have found that gold, silver, ticonium, vitallium and stainless steel are nontoxic while vanadium and copper are highly cytotoxic. [ED. NOTE: The authors unfortunately do not differentiate between the types of stainless steel, and this detracts considerably from the value of the article.]

Venable and Stuck<sup>763</sup> call attention to improvements in the strength and the flexibility of the new vitallium products made after the formula for vitallium was changed because the original metal was too brittle. They claim that the tensile strength of nails, screws or plates is unimportant. [ED. NOTE: This is a statement which is difficult to understand.] They advise the use of a wood or coach type of screw which does not taper except at its tip and suggest that the drill hole must be made the same size as the shank of the screw. [ED. NOTE: One of us (J. W. W.) believes that the size of the drill hole should vary with the density of the bone. In cancellous bone, a screw will hold much more securely if the drill hole is just small enough to allow the screw to be driven in with a reasonable amount of resistance but without the risk of twisting off the head.] The proper technic of inserting the screws is described, and the special need of proficiency in this exact and important type of craftsmanship is well stressed.

For internal fixation of fractures of the femoral neck Lorenzo<sup>764</sup> advocates the use of a rather complicated-looking lag screw arrangement requiring special but simple equipment for its insertion. Its particular merit seems to be that it produces positive pressure between the bone surfaces at the site of the fracture. [ED. NOTE: The chance that the bone surfaces may be held apart when the usual physiologic bone absorption at the fracture surface during repair occurs is not mentioned. Some of the author's illustrations which show the guide wire penetrating the floor of the acetabulum should be more carefully explained, as they certainly do not create a favorable impression. His advice to wait four or five days before fixation to allow shock to subside is open to question. It is the belief of most surgeons who employ hip nailing that early fixation is desirable to make the patient more comfortable

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762. Campbell, E.; Meirowsky, A., and Hyde, G.: Studies on the Use of Metals in Surgery: Comparative Determinations of Cytotoxicity of Certain Metals (Including Ticonium) in Fibroblast Culture, *Ann. Surg.* **114**:472-479 (Sept.) 1941.

763. Venable, C. S., and Stuck, W. G.: Three Years' Experience with Vitallium in Bone Surgery, *Ann. Surg.* **114**:309-315 (Aug.) 1941.

764. Lorenzo, F. A.: Molybdenum Steel Lag Screw in Internal Fixation of Fractured Neck of Femur, *Surg., Gynec. & Obst.* **73**:90-104 (July) 1941.

as soon as possible. This type of injury, while it is ordinarily extremely painful, is not usually associated with shock.]

*New Operations.*—Albee<sup>765</sup> has reported an interesting bone-drilling operation devised for the treatment of chronic ulcers in the lower part of the leg. Healing of ulcers that have responded to nothing else is reported in two thirds of all cases. No infection was encountered although the drill passed through the infected ulcers into the medullary cavity. [ED. NOTE: One wonders whether the improved care and the lack of weight bearing might not have been a contributing factor. The idea presented certainly has a great deal of merit and is apparently safe.]

Speed<sup>766</sup> reports on using vitallium caps on animal and human radial heads to insure the return of rotation. The author hopes by using this method to shorten the convalescence after excision of radial heads and to avoid trouble with the distal radioulnar joint so common in cases in which excision of the radial head has been necessitated. [ED. NOTE: The subject is most interesting but as the author admits is in the experimental stage. Further reports will be awaited.]

As advocated so extensively by Bunnell, the use of silver wire as a suture in secondary wound closure is urged by Payr.<sup>767</sup> Attention is called to the fact that the wire itself is an antiseptic and that if conditions require a stitch may be released by untwisting a wire.

Koontz and Shackelford<sup>768</sup> in a series of experiments on dogs have demonstrated that alcohol-preserved fascia and living fascia give the same results when used as a bone suture. [ED. NOTE: This does not seem reasonable, and it is hoped that this work will be checked by other investigators. It appears to be at variance with generally accepted facts.]

*Equalization of Length of Legs.*—In an excellent article Moore<sup>769</sup> brings up to date the present status of leg-lengthening operations. He reviews critically the cases of 19 patients operated on in the last twelve years who have reached growth maturity. With regard to gait, only 6 are considered to have been improved; nine were not improved, and 4 were made definitely worse. The author considers that weak hip mus-

765. Albee, F. H.: Bone Drilling in Resistant Chronic Ulcers: New Principle, *Am. J. Surg.* 54:605-608 (Dec.) 1941.

766. Speed, K.: Ferrule Caps (Vitallium) for Head of Radius, *Surg., Gynec. & Obst.* 73:845-850 (Dec.) 1941.

767. Payr, E.: Advantages of Silver Wire Suture in Wound Closure Compared with Delayed or Secondary Suture and Plaster Strapping, *Zentralbl. f. Chir.* 67:1958-1961 (Oct. 19) 1940.

768. Koontz, A. R., and Shackelford, R. T.: Comparative Results in Use of Living and Preserved Fascia as Suture Material in Bone, *Surgery* 9:493-502 (April) 1941.

769. Moore, B. H.: Critical Appraisal of Leg Lengthening Operation, *Am. J. Surg.* 52:415-423 (June) 1941.

cles and a weak quadriceps muscle account for most of the less satisfactory results. There were no cases of nonunion; infection of slight degree was observed in 1 case, and temporary nerve involvement was present in 2 cases. [ED. NOTE: This is an excellent summary of a hazardous surgical procedure that was at one time popular. It is well worth reading by the young enthusiastic surgeon contemplating a tibia-lengthening operation.]

Kofmann<sup>770</sup> has published a rather brief discussion of the various bone-shortening operations. He mentions various procedures, including his own autosynostosis operation, which consists of cutting a generous curved section apparently out of the lateral side of the shaft of the bone before transverse osteotomy across the shaft at the narrowest portion of this curve. He thus produces two pointed ends, one of which is slipped into the medullary cavity of the other. He emphasizes the simplicity of his technic and calls attention to the value of the shortening procedure in cases of finger contracture, manus vara, Volkmann's contracture and growth deformity. [ED. NOTE: The author unfortunately devotes little space to the details of the technic he has proposed.]

Harmon and Krigsten<sup>771</sup> discuss the surgical treatment of discrepancies of leg length. They emphasize the epiphysial arrest procedure on account of its simplicity, stressing, however, the need of accurate calculation, particularly as to which epiphysis is to be operated on and when during the period of growth the operation should be done. They sound a note also relative to the formidability of the leg-lengthening procedure which they consider much more hazardous than the shortening technic. They quote various authors who have studied the proportionate growth of the epiphyses of the lower extremities. They consider the growth to be approximately as follows: 12 per cent upper femoral; 40 per cent lower femoral; 28 per cent upper tibial, and 20 per cent lower tibial. [ED. NOTE: These figures seem reasonable and safe enough to be relied on in calculation. Exception might be taken to the statement that "leg shortening is the most exact and frequently indicated operation in . . . adolescence." After mature study one of us (J. W. W.) feels that during the adolescent growing period the growth arrest operation is the more certain, especially in view of the fact that the amount of growth stimulation associated with the shortening procedure is difficult to predict. Sometimes a net gain of only 50 per cent of the actual amount shortened can be finally recorded.]

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770. Kofmann, S.: Autosynostosis as Simple Method of Shortening the Bone, *J. Bone & Joint Surg.* **23**:159-161 (Jan.) 1941.

771. Harmon, P. H., and Krigsten, W. M.: Surgical Treatment of Leg Length Discrepancies, *Illinois M. J.* **79**:300-307 (April) 1941.



Two articles on the effect of roentgen irradiation on the epiphysis or, more accurately, the metaphysis [ED. NOTE: This term does not yet seem to be in common usage.] appeared during 1941. Judy<sup>772</sup> reports that small doses of roentgen radiation to the metaphysis apparently do not stimulate growth. An unsuccessful attempt was made to retard growth of the long leg in a child by fractional roentgen doses. Sufficient retardation was produced in 4 children to result in the appearance of definite transverse growth lines, but not enough was obtained to be of any practical use. This paper is a preliminary report only, and further experimentation with larger doses is to be done on animals.

Spangler<sup>773</sup> reported also the cases of 4 children in whom early closure of the epiphysis was attempted by fractional roentgen doses without definite success. The author admits that the treatments were given with "fear and trembling" and that the subject is still decidedly in the experimental stage.

[ED. NOTE: One of us (J. W. W.) was associated with Dr. Judy in his work. While it is believed definitely that sooner or later arrest of growth will be accomplished by roentgen irradiation, at present the factor of safety between serious soft tissue damage and effective exposure is too narrow. More definite information must be obtained by animal experimentation before further work on children can be attempted.]

## XX. RESEARCH

*Bone Growth, Repair and Metabolism.*—A considerable amount of experimental work regarding bone growth, repair and metabolism has been reported in the literature of 1941. The subjects investigated cover a wide range of interest and are rather loosely connected. Therefore, no attempt will be made to indicate by a blanket statement the degree of progress attained in any one direction.

*Vitamins and Bone Formation.*—Roche and Marcelet<sup>774</sup> state that the long bones and the flat bones present a different sensitivity to the action of vitamin D on disturbed alimentary factors. Only the long bones calcify normally when the diet is unbalanced in the course of growth; the flat bones present a marked demineralization persisting even to adult life. On the contrary, an abundant intake of balanced salts permits the

772. Judy, W. S.: Attempt to Correct Asymmetry in Leg Length by Roentgen Irradiation: Preliminary Report, *Am. J. Roentgenol.* **46**:237-240 (Aug.) 1941.

773. Spangler, D.: Effect of X-Ray Therapy for Closure of Epiphyses (in Correction of Asymmetry in Leg Length): Preliminary Report, *Radiology* **37**: 310-315 (Sept.) 1941.

774. Roche, J., and Marcelet, Y.: Comparative Sensitivity of Long Bones and Flat Bones to Action of Vitamin D and to That of Alimentary Saline (Calcium and Phosphorus) Disequilibrium, *Compt. rend. Soc. de biol.* **134**:280-282, 1940.

organization of fundamental osseous tissue and of phosphocalcific reserves, even in the absence of vitamin D, in the long bones, while the important deposition of salts in the flat bones takes place only in the presence of vitamin D. It appears, therefore, that the long bones fix salts preferentially as compared with the flat bones. The fact that this tropism of the long bones is much more marked in young animals suggests the hypothesis that endochondral ossification participates more actively than membranous ossification; the great affinity of conjugating cartilage for salts seems to support this view.

The authors state that Sherman, Stiebeling and Fischmann have demonstrated that the role of vitamin D in ossification is important on the one hand because of its action in the absorption of salts carried by the diet and on the other hand because of its action in the organization of fundamental osseous tissue. The first action manifests itself equally in growing animals and in adult animals, while the second can be effective only before the growth of the skeleton is completed.

Mellanby<sup>775</sup> reports experiments with young dogs to determine the effect of vitamin A deficiency on the growth of bone. In previous publications he has presented evidence of the widespread degeneration of the central and the peripheral nervous system, especially in young animals brought up on diets deficient in vitamin A and carotene and rich in cereals.

All or nearly all bones in the body are affected by these vitamin A-deficient diets, but this report deals mainly with the gross changes in the bones of the skull and of the vertebral column and the effect which these changes have on the nervous system.

If the administration of the special diets is started when puppies are 6 to 9 weeks of age, the animals' incoordination of movement and other signs of abnormal behavior and appearance develop two to four months later, and after four months the abnormality may be great. In fully grown animals, on the other hand, although vitamin A deficiency affects bone structure, the action is slow, and many months or even a year or more may be required to produce noticeable changes.

A comparison of mesial sagittal surfaces of the skull of 2 litter mates, one of which had a diet containing much vitamin A and the other a diet deficient in the vitamin, shows some of the regions which are especially subject to overgrowth of bone. The bones showing the most overgrowth are those surrounding the cerebellum, the medulla oblongata and the pons varolii. In particular all parts of the occipital bone are greatly enlarged. Passing forward, the parietal bone is also much thickened in its posterior

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775. Mellanby, E.: Skeletal Changes Affecting Nervous System Produced in Young Dogs by Diets Deficient in Vitamin A. *J. Physiol.* 99:467-485 (June 30) 1941.

part, but this thickening becomes less as it approaches the frontal bone. The effect of this overgrowth is to press on the cerebellum and the medulla and alter their shape. The cerebellum is flattened on its dorsal surface, and its posterior surface is indented just above the foramen magnum. The medulla is similarly compressed, and the fourth ventricle and the aqueduct of Sylvius are narrowed and reduced in capacity.

The kind of differences observed in the shape and the texture of the bones of the skull of normal and vitamin A-deficient dogs can be seen also in the bones of the vertebral column. All the normally clearcut outline of the vertebrae disappears in the vitamin A-deficient animals. There seems to be little or no increase in the over-all dimensions of each vertebra, but all the processes, including the arches and the articular processes, are thickened to a greater or a lesser extent.

Gross sections of the femoral shafts were studied to determine the histologic changes occurring in vitamin A-deficient animals. There was a reduction in the diameter of the marrow cavity owing to an invasion of this cavity by cancellous bone.

The actual bone formed in the vitamin A-deficient animal is probably not far removed in character from normal bone. There is no demonstrable increase in osteoid tissue. It is the gross arrangement of the bone which is so strikingly changed. It is probable, therefore, that the main effect of vitamin A on bone growth is to control the activity and the number of osteoblasts and osteoclasts, primarily those associated with the bone marrow but also to a lesser degree the same cells in the subperiosteal region. In the absence of the vitamin these cells become more active, but the change seems to be one only in intensity of cell activity but not in the function of the cells.

In the presence of vitamin A deficiency chemical examinations show that there is practically no change in the actual amount of calcium in the bones but that there is an increase in the fat content of the bones. [Ed. NOTE: This is an extremely valuable and interesting study. It should stimulate further investigations in this field of research.]

*Epiphyses and Bone Growth.*—In investigations on epiphysial growth, Ingalls<sup>776</sup> has selected the tibial epiphysis of albino rats receiving an adequate diet of cereals, minerals and vitamins for study. A new method of taking roentgenograms of the knee with the tube directly over the joint and with the use of dental film has been found to give sharper details, especially when the bone is denuded of soft parts. Some bones were impregnated with silver; this gives sharp contrasts in the roentgenograms. The author describes a modification of the Goworsi method of preparation of tissue sections. The anatomy of the epiphysial plate

776. Ingalls, T. H.: Epiphyseal Growth: Normal Sequence of Events at Epiphyseal Plate, *Endocrinology* 29:710-719 (Nov.) 1941.

is reviewed. The following factors influencing growth are mentioned: nutritional (calcium, phosphorus, vitamins D and C); endocrine (pituitary, thyroid, parathyroid, sex gland), and toxic (lead, phosphorus, bismuth, fluorine). Disturbances of any of these factors register changes within a few days at the epiphyses, and the diagnosis (e. g., scurvy, rickets, lead and phosphorus poisoning) can be made by the histologist and roentgenologist.

Ingalls summarizes briefly: The cartilage is composed of germinal, proliferating and degenerating layers. The metaphysis is composed of a rind of new bone laid down by osteoblasts around the calcified matrix of degenerated cartilage cells. In the interstices of the metaphysis are capillaries, osteoblasts and osteoclasts, developing and remodeling the true bone. Calcium depositions have been demonstrated in both the longitudinal and the transverse septums of the matrix of the degenerating cartilage cells. [ED. NOTE: Some authors have previously concluded that calcium salts are deposited only in the longitudinal septums.] The deposition of calcium salts in the ground substance appears to follow the death of the cartilage cells.

Ingalls and Hayes<sup>777</sup> have studied the effect of removal of adrenal and pituitary glands on the epiphysis of young rats. There was found to be an absence or inhibition of metaphysial bone formation. There was a decrease in the number of osteoblasts and in the amount of osteoid material present. These features are not the same as those recorded by some authors, namely, "features exactly analogous to those exhibited at the end of the normal growth period." The authors believe that there is widespread atrophy of the cartilage and the primary spongiosa and that there occurs halisteresis of the whole bone which is distinctly pathologic.

Banks and Compere<sup>778</sup> have performed experiments on rats and on rabbits to study the effect of injury to the epiphysial cartilage on bone growth and to confirm or disprove Selye's theory that "the growth of very young bones is largely independent both of the pituitary growth hormone and of the derivatives of epiphyseal cartilage anlage." Various gradations of damage were done to the epiphyses and the cartilage plates. The results of these investigations largely refute the theory of Selye. It was demonstrated: (1) that in resection of all or half of the epiphysis the resected portions are not restored and the longitudinal growth of the epiphysis is arrested and (2) that if the epiphysial cartilage plate is injured or resected the longitudinal growth of the shaft is either partly or completely arrested.

777. Ingalls, T. H., and Hayes, D. R.: Epiphyseal Growth: Effect of Removal of Adrenal and Pituitary Glands on Growing Rats. *Endocrinology* 29:720-724 (Nov.) 1941.

778. Banks, S. W., and Compere, E. L.: Regeneration of Epiphysial Cartilage: Experimental Study, *Ann. Surg.* 114:1076-1084 (Dec.) 1941.

Siegling<sup>779</sup> proves most conclusively that no growth in length of bone occurs from the epiphysial cartilage side of the epiphysis. Growth in the epiphysis takes place solely from endochondral ossification. This is substantiated by the concentric growth contours in the epiphyses of children who have had severe illnesses which seem to start at one end of the epiphysial line and end at the other. [ED. NOTE: This is an excellent article.]

Aries<sup>780</sup> states that textbooks of histology and embryology have to the present described longitudinal growth of bone as taking place by apposition at the diaphysial side of the epiphysial plate in the form of lines paralleling the epiphysial plate. Aries has given injections of alizarin red to 52 albino rats and killed them at intervals. The growth lines showed that longitudinal growth of long bones takes place in the form of superimposed serial cones within the diaphysial portion of the shaft, the bases of which are the epiphysial plate at any one given time. The periosteum deposits bone on the circumference of the shaft only and does not contribute to longitudinal growth. The distal end of the femur grows faster than the proximal end. The longitudinal growth and the growth in width follow a growth gradient which diminishes with age.

The irregularity in bone structure of rapidly growing epiphyses, particularly about the knee, seen in children in the early walking age is discussed by Sontag and Pyle.<sup>781</sup> They call this condition "disseminated calcification." The authors feel that it is influenced by thyroid function but give no satisfactory explanation to justify this belief. When it appears in other epiphyses during the second year of life or a little before, it is frequently considered unjustifiably as a pathologic process. It seems to be associated with early weight bearing. [ED. NOTE: Many who have seen this condition and have been somewhat at a loss to explain it will be enlightened by this article and especially by the statement that "it is a normal occurrence in rapidly developing epiphyses and indicates no pathology, being solely a maturational and growth factor."]

Stammel<sup>782</sup> describes two cases of multiple striae parallel to the epiphyses in the alae of the ilia. In the skulls of these patients the base appeared sclerotic; the bodies of the vertebrae were sharply outlined, and within the bodies were found contours of smaller well shaped bodies. In

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779. Siegling, J. A.: Growth of Epiphyses, *J. Bone & Joint Surg.* **23**:23-36 (Jan.) 1941.

780. Aries, L. J.: Experimental Analysis of Growth Pattern and Rates of Appositional and Longitudinal Growth in Rat Femur, *Surg., Gynec. & Obst.* **72**:679-689 (April) 1941.

781. Sontag, L. W., and Pyle, S. I.: Variations in Calcification Pattern in Epiphyses: Nature and Significance, *Am. J. Roentgenol.* **45**:50-54 (Jan.) 1941.

782. Stammel, C. A.: Multiple Striae Parallel to Epiphyses and Ring Shadows Around Bone Growth Centers, *Am. J. Roentgenol.* **46**:497-505 (Oct.) 1941.

the lower third of both femurs there was a definite fusiform swelling and many transverse bands parallel to the epiphysis. The head of the fibula showed similar striations. The scaphoid, the third cuneiform and the cuboid bone showed similar markings, but the other tarsal bones were negative. Both cases were similar in every respect except that in 1 there were striations of some of the teeth.

Stammel concludes that something occurred during the period of rapid growth of the bones involved that caused temporary delay or cessation of growth. The most probable condition that may cause this is unexplained periods of thyroid hypofunction. Repeated mild unrecognized attacks of scurvy may also be a plausible explanation. Also, it is possible that as children the patients may have ingested enough lead or other metal to be deposited in the bones but not enough to cause severe symptoms.

Lastly, it is not improbable that the condition may have been atypical mild undeveloped Albers-Schönberg disease, even though there was no tendency to fractures and no alteration in the blood picture in either case.

*Ossification Centers.*—Bruce<sup>783</sup> surveys the time and the order of appearance of ossification centers and their development in a series of embryonic rabbit skulls. The embryos were taken at intervals during gestation, beginning at sixteen days, two hours after copulation and extending to birth at thirty days. The method consisted of placing embryos after removal from the uterus in solution of potassium hydroxide long enough to soften the skin and the flesh. The writer states that if the embryo has been left in solution of potassium hydroxide for just the right length of time the skin becomes elastic and may be pulled off without injury to the bones. She concludes her study by observing that new ossification centers cover a period of twelve days from the sixteenth day, when the mandible appears, to the twenty-eighth day, when the petrous portion of the temporal complex starts to ossify. Ossification begins either in the central body of the bone, later spreading to the processes, or in processes which eventually grow together to form a central body. Those bones which develop in the latter way or those which develop no subsequent processes are the ones which acquire their characteristic shapes the earliest. A graph is presented showing the comparative time of appearance of ossification centers in several skulls in percentage of respective gestation periods. In animals having a shorter intrauterine period ossification occurs relatively later, and these animals are born at a relatively younger skeletal age. The order of appearance of the bones of the skull is about the same in rabbit, man, rat and mouse.

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783. Bruce, J. A.: Time and Order of Appearance of Ossification Centers and Their Development in the Skull of the Rabbit. *Am. J. Anat.* 68:41-67 (Jan.) 1941.

*Mobilization of Bone Salts.*—Walter, Van Slyke and Hufnagel<sup>784</sup> give a brief preliminary report on the effect of electrolysis in mobilizing and depositing calcium in an experimental animal. Two platinum bands each 2 mm. wide were wrapped subperiosteally around the femur of an anesthetized rabbit, the bands being about 1 cm. apart. Roentgenographic studies revealed transverse bands of decreased density underlying the region once occupied by the positive electrode. There was no gross reaction about the negative electrode. Control experiments showed that the electrodes themselves did not produce the changes described. It is believed that the response is dependent entirely on mobilization of the calcium from the bone.

The purpose of the experiments of McLean and Bloom<sup>785</sup> was to demonstrate histologically by a special technic the mobilization of bone salts and the relation of osteoclasts and other bone cells to this phenomenon. They conclude that the organic matrix of bone and bone salts are absorbed simultaneously by local cellular action and not by a phagocytic function of osteoclasts. There is no evidence from these studies that absorption of bone matrix occurs as a reaction to decalcification.

*Delayed Ossification.*—Cretin,<sup>786</sup> studying the histogenesis of osseous tissue in delayed consolidation, concludes: (1) that osseous construction is due to osteoblasts which receive their nutrition from muscle; (2) that for this reason it is impossible to separate the study of bone from that of muscle, and (3) that repeated hemorrhages about a fracture site which cannot be absorbed (perhaps in some instances owing to muscle injury) is a definite factor in producing delayed union. [ED. NOTE: This investigative evidence certainly has clinical value and may explain some cases of delayed union, especially in the shaft of the femur, where muscle usually completely surrounds the fracture site.]

*Effect of Manganese on Bone Growth.*—Studies were undertaken by Barnes, Sperling and Maynard<sup>787</sup> to determine whether any bone abnormality could be noted in the rat given a diet low in manganese. They have been unable to demonstrate any abnormal development of the tibia in the albino rat raised on a diet low in manganese provided the rat is normal at 21 days of age. The rat differs from the chick in being much

784. Walter, C. W.; Van Slyke, K. K., and Hufnagel, C.: Mobilization and Deposition of Calcium by Electrolysis: Preliminary Report, *Surgery* 10:145-146 (July) 1941.

785. McLean, F. C., and Bloom, W.: Calcification and Ossification: Mobilization of Bone Salt by Parathyroid Extract, *Arch. Path.* 32:315-333 (Sept.) 1941.

786. Cretin, A.: Histogenesis of Bone Tissue in Light of Study of Delayed Consolidation: Role of Muscles, *Presse méd.* 48:996-999 (Dec. 11-14) 1940.

787. Barnes, L. L.; Sperling, G., and Maynard, L. A.: Bone Development in Albino Rat on Low Manganese Diet, *Proc. Soc. Exper. Biol. & Med.* 46:562-565 (April) 1941.

less sensitive to a diet low in manganese. Only 2 cases of abnormal tibias occurred among a total of 16 rats born of females reared on a diet low in manganese. The limited data on rats from females reared on a diet low in manganese suggest that the growth of the female is impaired while that of the male is not.

*Effect of Fluorides on the Skeleton.*—Volker, Sognnaes and Bibby<sup>788</sup> have carried out a series of experiments on the biochemistry of fluorides, using radioactive fluorine. The blood fluoride level was found to decrease as the skeletal level rose, and the amount of rise paralleled the blood supply to that particular osseous structure.

Figures reveal that the greatest proportion of salivary and urinary fluoride was excreted during the first thirty minutes, i. e. the period when the blood level was highest. In discussing the results, the writers note that the high fluoride deposition in the bony skeleton is probably related to the observation that the addition of fluoride to the rachitogenic diet decreases the severity of experimental rickets.<sup>789</sup>

*Endocrine Secretions and Their Effect on Growth, Maturation and Degeneration of Bone.*—The effects of endocrine preparations on growth, maturation and degeneration of bone when administered to various experimental animals have been recorded during the past year. Some authors have attempted to explain mechanisms, and some have suggested possible correlation to human disease. Estrogen was shown in various experiments to increase phosphatase in the femur of the rat, increase serum calcium in ducks, increase bone formation in ducks, increase osteoblastic activity and increase bone ash. Solution of parathyroid in small repeated doses caused a temporary increase of phosphatase of the diaphysis and no change in the epiphysis of the rat. A large dose caused an increase which was followed by a decrease in the diaphysis and a decrease in the epiphysis of the rat. Solution of parathyroid did not have an effect on serum fat or bone formation in chicks. Extracts of adrenal cortex caused a decrease in phosphatase in the diaphysis and the epiphysis of the rat. Progesterone caused an increase in phosphatase in the femur of the rat. It promotes hyperplasia of cartilage and inhibits deposition of new bone and retrogressive changes in cartilage and bone. Testosterone propionate causes the os penis and ischial tuberosities to appear and develop faster in rats. Testosterone propionate accelerates growth, maturation and degeneration in female mice. Vitamin D presents visual or morphologic rickets, but if the criterion for judging the presence

788. Volker, J. F.; Sognnaes, R. F., and Bibby, B. G.: Distribution of Radioactive Fluoride in Bones and Teeth in Experimental Animals, *Am. J. Physiol.* **132**:707-712 (April) 1941.

789. Morgareidge, K., and Finn, S. B.: Effect of Fluorine on Activity of Vitamin D in Rachitic Rats, *J. Nutrition* **20**:75-84 (July) 1940.



of rickets is enlarged to include bone ash studies (in rats), phosphatase must be added to prevent rickets. Estrone (theelin) and its possible relation to osteitis fibrosa cystica are considered in this study.

Williams and Watson<sup>790</sup> carried out experiments to determine whether the sex hormones influence the phosphatase content of bone. Single large nonlethal doses were administered to albino rats of approximately 50 days of age. The animals were killed at intervals thereafter, and the phosphatase content of the femurs was analyzed.

The results may be summarized briefly as follows: Progesterone, testosterone propionate and estradiol benzoate tend to increase the phosphatase content, the effect being most marked in the epiphyses following use of testosterone propionate. Thymus extract causes a moderate increase, and the observations of others that thyroxin causes an increase in the phosphatase content of bone have been confirmed.

Williams and Watson<sup>791</sup> have attempted to explain the apparent salutary effects as well as the accompanying reduction of serum phosphatase following the administration of extracts of adrenal cortex to persons with Paget's disease of the bone and chronic arthritis. The possibility that there may be a modification in the production of the enzyme is the subject of the present investigation. Two types of experiments were performed; these were called the acute and the chronic type. In the former the effects of single large doses and in the latter the effects of small repeated doses of extract of adrenal cortex and solution of parathyroid on the phosphatase content of femurs of rats were determined.

The chronic experiments revealed that small repeated doses of solution of parathyroid produced a temporary increase in the phosphatase of the diaphyses without any change in that of the epiphyses. In the acute experiments this substance caused an increase followed by a decrease in the phosphatase of the diaphyses, while only a decrease in the phosphatase of the epiphyses was noted.

Extracts of adrenal cortex caused a reduction in the phosphatase of both diaphyses and epiphyses, the effect being more marked in the latter. Corticosterone and the compound E of Kendall (17-hydroxy, 11-dehydrocorticosterone), adrenal cortical substances, most closely approximated the effect of the whole cortical extract in reducing phosphatase contents of bones. No attempt is made to explain the mechanism underlying these changes, but there is thought to be a possible correlation

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790. Williams, H. L., and Watson, E. M.: Influence of Hormones upon Phosphatase Content of Rat Femur: Effects of Adrenal Cortical Substance and Parathyroid Extract, *Endocrinology* 29:258-261 (Aug.) 1941.

791. Williams, H. L., and Watson, E. M.: Effects of Adrenal Cortical Substances and Parathyroid Extract on Phosphatase Content of Rat Femurs, *Endocrinology* 29:250-257 (Aug.) 1941.

between these findings and the results of the clinical use of extract of adrenal cortex in the treatment of Paget's disease.

The Silberbergs<sup>792</sup> have investigated the effect of progesterone on changes taking place in cartilage and bone during growth and aging. Seventy guinea pigs were used; these were given subcutaneous injections of progesterone on six days of the week for periods of one, two, four, six and eight weeks. Sections were made from the upper part of the tibia, the knee joint and the chondro-osseous junctions of several ribs.

Progesterone promotes slight hyperplasia of the cartilage cells which may be interpreted as a stimulating effect; however, at the same time it inhibits the deposition of new bone. Progesterone maintains the juvenile character of cartilage and bone by inhibiting retrogressive changes in the tissues. Progesterone inhibits the conversion of immature into mature bone, and in the ribs it inhibits atrophy, degeneration and calcification. These changes were almost the opposite of the acceleration of age changes following the use of estrogen.

In order to study more in detail the cellular changes which take place after administration of estrogen, Bremer<sup>793</sup> treated young white rats with theelin in varying amounts and over varying periods. The results noted were practically the same as those noted after the administration of solution of parathyroid.

The first histologic evidence of the beginning of osteitis fibrosa is the changing of osteoblasts from their normal shape to spindle cells and the uniting of neighboring cells by connecting strands, the whole forming a mesenchymal tissue. The changes are first noticeable on the peripheral bone spicules just beneath the inner cellular layer of the periosteum in the subepiphysial region and are accompanied by absorption of the newly formed bone and local increase of osteoclasts; this process spreads inward along the trabeculae. The same process takes place normally in growing long bones and leads to the molding and the shaping of the slender shafts beneath the wider broader articular ends. Normally the destruction of bone is strictly limited, taking place in an orderly manner along wide curves that sweep from the edge of the broad epiphysis to the surface of the narrower shaft, cutting diagonally across the tips of the newly formed bone trabeculae, which are oriented in a vertical direction following that of the vertical rows of cartilage cells in the epiphysial line. The extent of this process is governed by a true balance between estrogen and androgen, which are normally present in both male and female persons. These two principles are known to be

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792. Silberberg, M., and Silberberg, R.: Effect of Progesterone (Corpus Luteum Hormone) on Growing Cartilage and Bone in Immature Guinea Pigs. Arch. Path. 31:85-92 (Jan.) 1941.

793. Bremer, J. L.: Osteitis Fibrosa Localisata: Experimental Study. Arch. Path. 32:200-210 (Aug.) 1941.

mutually antagonistic in their action. In rats treated with theelin the balance is disturbed, and the destruction becomes irregular and excessive. Osteitis fibrosa cystica is not due to an abnormal process but merely to an abnormal excess of a process which is itself normal in the molding of young bones.

In an attempt to reproduce in the bones of the rat conditions similar to those in the older normal chick, young white rats just weaned were treated with varying amounts of theelin for ten to twenty days and then allowed to live without injections for a further variable period. In a few rats significant changes were found. These consisted mainly of isolated areas of mesenchyme or cartilage in the subepiphysial region of the humerus. The author suggests that a true cyst might arise by the degeneration and central liquefaction of such an isolated mass or by the erosion of vessels and consequent hemorrhage.

An experiment was carried out by Turner, Lachmann and Hellbaum<sup>794</sup> in which castrated and uncastrated rats were treated by varying dosages of testosterone propionate. The results are reported as follows: Prolonged injections of testosterone propionate, even when begun one day after birth, did not significantly alter skeletal maturation or body growth in rats. The appearance of the os penis and the ischial tuberosity epiphyses were hastened. However, the osseous progress of untreated animals was such that at eighty-seven days there were no demonstrable skeletal differences between these and the treated rats.

The Silberbergs<sup>795</sup> distinguish three main phases of skeletal growth. In their strain C mice the first phase, lasting to the end of the fourth month, is characterized by proliferation of the epiphysial cartilage. The second phase, ending with the first year, is characterized by retrogressive changes in the epiphysial cartilage and an increase in density and thickness of the bones. The third period sees the ossification of the epiphysial cartilage and the resorption of bone in the shaft.

The time factor of these phases was used to study the influence of endocrine preparations on cartilage and bone growth. Anterior pituitary extract caused stimulation of cartilage proliferation; this was followed by shortening of the proliferative phase. With pituitary transplants an inhibitory effect is first noted, but this is followed by a prolongation of the proliferative phase. The processes of resorption of bone were more pronounced by the action of extracts; the formation of bone was more accentuated by the action of transplants.

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794. Turner, H. H.; Lachmann, E., and Hellbaum, A. A.: Effect of Testosterone Propionate (Androgen) on Bone Growth and Skeletal Maturation of Normal and Castrated Male Rats, *Endocrinology* 29:425-429 (Sept.) 1941.

795. Silberberg, M., and Silberberg, R.: Effects of Hormones on Skeleton of Mice, Guinea Pigs and Rats, *Endocrinology* 29:475-482 (Sept.) 1941.

In dogs, guinea pigs, rats and mice thyroid extract caused a marked stimulation of proliferation of cartilage; this was followed by a sharp decline and an intensification of processes of degeneration and resorption. Injections of potassium iodide caused the same reactions, but proliferation was less active and degeneration less marked. Injections of solution of parathyroid caused degeneration of cartilage without any preceding proliferative stimulation.

Estrogen and testosterone inhibit cartilage proliferation and temporarily the resorptive processes of cartilage and bone. Subsequently retrogressive changes occur more rapidly than normally. Estrogen is more active in both aspects than testosterone.

Gonadectomy and progesterone induce a primary delay of onset and progress of skeletal gain, but eventually in late stages this is neutralized by an intensification of the process of resorption. The effects of different endocrine principles on cartilage and bone vary in various species, in various strains in the same species and according to the age of the animal used.

Day and Follis<sup>796</sup> gave subcutaneous injections of estradiol benzoate at intervals varying from seventeen to one hundred and twenty-five days to more than 200 rats that ranged from 30 to 650 days of age. By means of histologic roentgen and chemical technics the effects of the estradiol benzoate on the skeleton were studied.

The histologic changes that were noted were mainly an increase at the growing ends of the bones. These changes were noted as early as seventeen days after the treatment was started. The skeletal changes were greater in female than in male rats. The authors' conclusions are that estrogen causes a decrease in normal destruction of bony trabeculae, just beneath the cartilage-shaft junction. At the cartilage-shaft junction they noted also an increase in osteoblastic activity. This was not noted at any other point. They conclude that this activity increases the density of the epiphyses and thus accounts for the increase in concentration of ash in the bone as a whole.

The Silberbergs,<sup>797</sup> in another study, used 36 virgin mice 2 to 4 weeks old. These mice received injections of testosterone propionate weekly for periods of two weeks, one month, two months, three months, four months, sixteen months and nineteen months. They found that in growing female mice the testosterone propionate accelerates the aging

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796. Day, H. G., and Follis, R. H., Jr.: Skeletal Changes in Rats Receiving Estradiol Benzoate (Estrogen) as Indicated by Histological Studies and Determinations of Bone and Serum Calcium and Phosphate. *Endocrinology* **28**:83-93 (Jan.) 1941.

797. Silberberg, M., and Silberberg, R.: Response of Cartilage and Bone of Growing Mice to Testosterone and Propionate (Androgen). *Arch. Path.* **32**:85-95 (July) 1941.

of the epiphysial cartilage and that proliferation of the resting and columnar cells and their differentiation into hypertrophic cartilage cells and sclerosis, hyalinization and calcification of the cartilaginous matrix are intensified. The authors state that high single doses of testosterone administered over short periods are more effective in producing the changes than small doses over longer periods.

Lurie and Hertzman<sup>798</sup> report on the effect with regard to linear bone growth of the treatment with chorionic gonadotropin of undescended testicles and genital underdevelopment in 23 cases. They conclude that an average gain in height above the normal expectancy occurs in almost half of the cases. They do not feel that the preparation is dangerous to use since it apparently does not produce premature closure of the epiphyses or retard linear growth. [ED. NOTE: It is difficult to correlate this claim, however, with the warning given later in the paper that too prolonged treatment tends to advance the bone age.]

*Muscles.*—A review of the literature on muscles for the year 1941 reveals little of unusual significance aside from certain observations made on the subject of poliomyelitis. Apparently the muscular involvement in this disease is the result not only of a pathologic condition in the anterior horn cells but also of associated factors which contribute to loss of function. Most important of these is muscle spasm. This observation, emphasized by Sister Kenny and confirmed by observers at the Children's Hospital, Iowa City, may have an important bearing on the treatment of this disease.

The ineffectiveness of electric current in the treatment of experimentally induced muscular paralysis has been demonstrated. Further evidence has been produced that in lower animals transplanted muscles are unable to perform new functions and that the reflex activity of the muscle shows no alteration of activity. Crossing nerves to antagonistic muscles has no effect in modifying the inherent specific property of the nerve induced by the original muscle. The intravenous injection of potassium chloride appears to delay the onset of fatigue.

*Vitamins and Muscular Dystrophy.*—Muscular lesions have been observed by Krakower and Axtmayer<sup>799</sup> in rats given vitamin A-free diets to resemble those of muscular dystrophy due to a lack of vitamin E. Since vitamin A-free diets do not contain vitamin E, the authors have determined whether the muscular lesions are due to deficiency of vitamin

798. Lurie, L. A., and Hertzman, J.: Linear Growth and Epiphysial Closure: Effect of Treatment with Chorionic Gonadotropic Substance; Twenty-Three Cases, *J. Clin. Endocrinol.* 1:717-725 (Sept.) 1941.

799. Krakower, C., and Axtmayer, J. H.: Effect of Alpha-Tocopherol on Lesions of Skeletal Muscles in Rats on Deficient Diets, *Proc. Soc. Exper. Biol. & Med.* 45:583-586 (Nov.) 1940.

A or to lack of vitamin E. In one series of experiments they gave 17 young rats vitamin A-free diets. The mothers of these rats had been given vitamin A-free diets from the fourteenth day to the twenty-eighth postpartum day, when the rats were weaned. Eight of the 17 rats were fed 1.5 mg. of alpha tocopherol in olive oil weekly, the remaining 9 control rats were fed olive oil alone. A second series of rats, which were also weaned at twenty-eight days but whose mothers had been given a diet of Purina dog chow, were placed on a vitamin A-free diet. Eight were given weekly subcutaneous injections of 5 mg. of alpha tocopherol acetate, and the remaining 9 were left as controls. All animals either were killed or died, and histologic section was made. The authors found that muscular lesions hitherto described in connection with vitamin A deficiency in rats can be prevented by the administration of alpha tocopherol and hence are not related to the vitamin A-deficient state. Vitamin E or alpha tocopherol should form a part of the basal diet used to produce vitamin A deficiency in rats.

*Neuromuscular Studies.*—Sperry<sup>800</sup> studied the effect of crossing nerves to antagonistic muscles in the hindlimb of rats with particular regard to the phenomenon of modulation of nerve by muscle. Modulation is described by Weirs as follows: When a nerve is severed from its muscle and forced to regenerate into a foreign muscle, the nerve cells under the influence of the new muscle undergo a process of cell modulation, losing the specific properties induced by the original muscle and acquiring those specific to the new muscle. Various attempts at training all failed to induce reeducation. Postmortem examination and physiologic tests showed that nerve regeneration had been as intended and that sensory as well as motor fibers had reinnervated the muscles. Severance of the crossed nerves abolished the reversed movement. Control animals similarly operated on except that the nerves were reconnected to the original muscles showed foot movement in normal phase in all activities.

The right and left sciatic nerves of 11 dogs were severed by Molander and Steinitz<sup>801</sup> and immediately sutured; after this both hindlimbs were placed in casts. The gastrocnemius muscles of both legs were tested for ability to contract to the faradic and the galvanic current. Treatment was given to one leg, the other serving as a control, twice daily for six weeks with a current adjusted to just produce visible contractions.

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800. Sperry, R. W.: Effect of Crossing Nerves to Antagonistic Muscles in Hind Limb of Rat, *J. Comp. Neurol.* **75**:1-19 (Aug.) 1941.

801. Molander, C. O., and Steinitz, F. S.: Effect of Galvanic Current on Paralyzed Muscle: Experimental Study on Dog, *Arch. Phys. Therapy* **22**:154-160 (March) 1941.

Paralyzed muscles did not respond to the faradic current in any case. The treated muscles showed no less loss of weight than the others. In 6 of 9 cases there was slightly less pronounced histologic evidence of degeneration. The untreated muscles exhibited a greater responsiveness to the galvanic current than the treated muscles, but both became steadily less sensitive to stimulation as the experiment progressed. Histologic sections revealed no difference in the changes in the sciatic nerves of treated and untreated gastrocnemius muscles. There is no evidence that paralyzed limbs are benefited by electrical stimulation. It still remains to be demonstrated whether such benefits can occur in paralyzed limbs in cases of poliomyelitis.

Buchthal and Clemmesen<sup>802</sup> have determined the electrical behavior of the muscle by action potentials which represent innervation impulses but not the contractions themselves. In the resting, fully relaxed muscle no potential oscillations exist. When electromyograms were taken of muscles, in certain cases a permanent rest activity was found. The activity was of an intensity similar to that produced by moderate involuntary contractures. The peripheral sensory receptors were paralyzed by procaine hydrochloride injected subcutaneously; however, the rest activity remained unchanged. Intramuscular injections of procaine hydrochloride caused at first a decrease in the rest activity and then finally complete disappearance. The authors therefore believe that the phenomenon of rest activity is connected with the sensory receptors of the muscle.

In a series of 46 patients studied by means of electromyography in whom typical conditions affecting muscle and organic nervous disease were present, 8 patients showed rest activity. The authors believe that palpable conditions affecting muscle can be arranged in two groups by means of electromyography: the first group, in which the electromyogram is the same as that of a normal muscle; the second group, in which the electromyogram of the resting muscle shows permanently interfering action potentials which correspond to moderate muscle contraction. Intramuscular injections of procaine hydrochloride, quinine and calcium as well as intravenous injection of calcium stopped this rest activity. The authors interpret these results as indicative of a permanent irritation of the proprioceptive receptors of the respective muscle, the cause of which is not yet known.

Weiss and Brown<sup>803</sup> have studied 20 cases (18 cases of poliomyelitis and 2 of spastic paralysis) by means of the electromyographic method in

802. Buchthal, F., and Clemmesen, S.: Differentiation of Palpable Muscle Affections by Electromyography, *Acta med. Scandinav.* **105**:48-66, 1940.

803. Weiss, P., and Brown, P. F.: Electromyographic Studies on Reoordination of Leg Movements in Poliomyelitis Patients with Transposed Tendons, *Proc. Soc. Exper. Biol. & Med.* **48**:284-287 (Oct.) 1941.

which transplantation of the biceps femoris to the extensor side of the knee joint was done. In their preoperative studies the authors observed that steady activity of the weak quadriceps muscle during flexor as well as extensor phases was present and seemed to be characteristic of coordination in patients with poliomyelitis in contrast to normal persons and patients with spastic paralysis. The biceps operates in the flexor phase only. Postoperative results indicated that when the leg operated on was removed from the cast for the first time no activity of the transplant was observed. Soon, however, the transplant began to show activity, at first in the flexor phase and after a few trials in the extensor phase as well. The transplant continues for some time to act in both flexor and extensor phases, and there is no evidence of automatic resumption of reciprocal innervation. After a further practice period of varying duration the transplant begins to be admitted during flexor actions. Relapses into the old flexor association may occur even years after the operation. These relapses seem to be favored by fatigue, lack of concentration and automaticity of movement. Their occurrence supports the view that the adjusted use of the transplant is not based on the substitution of a permanent extensor association for its former flexor association in the elementary motor mechanisms but rather on the development in higher centers of a new type of action which can effectively override the innate coordinative associations without abolishing them. This corroborates the distinction between lower, rigid and higher plastic systems in the control of coordination suggested by earlier observations.

Watrous and Olmsted<sup>804</sup> have studied the characteristics of reflex activity in a series of 5 dogs and cats in which various muscles were transplanted and present kymographic tracings to illustrate their findings. For example, the soleus muscle of a cat, an extensor, was transplanted to a flexor position. After decerebration typical exaggerated tone appeared in the soleus in spite of its flexor position and stimulation of the ipsilateral posterior tibial nerve caused inhibition of this tone. Similar studies were made after transplanting the peroneus longus muscle of a dog, a flexor muscle, to an extensor position.

The authors found that when tested by reflex activity the isolated responses of translocated muscles of the hindlimb of the adult cat and dog and of the translocated superior oblique muscle of the rabbit showed no alteration in function, even when as long as four months was allowed for readjustment.

[ED. NOTE: This work offers further evidence of the inability of transplanted muscles to perform new functions in the lower animals.]

804. Watrous, W. G., and Olmsted, J. M. D.: Reflex Studies After Muscle Transplantation, *Am. J. Physiol.* **132**:607-611 (April) 1941.



*Biochemical Studies of Muscles.*—Hoff, Winkler and Smith<sup>805</sup> have studied the effect of the intravenous injection of potassium chloride on fatigued muscle. They have found that the normal marked reduction in the height of muscular twitches as recorded on a myograph after repeated stimulation of the muscle either directly or through its nerve supply is prevented by the slow intravenous injection of isotonic solution of potassium chloride. They suggest that since potassium is known to be liberated from muscles during the type of muscular activity described this may be a factor responsible for the decrease in the intensity of contractions in fatigue. They further suggest the hypothesis that the mechanism of the restoration of the vigor of contraction of fatigued muscle may consist in the replacing of potassium previously lost during the development of fatigue.

The efficiency of muscular work has been found to be increased if the work is interrupted by regular and short pauses of rest.

Certain aspects of previous experimental work with vitamin A are subject to severe critical reevaluation since it has been shown that the standard vitamin A-deficient diets are likewise deficient in vitamin E.

Further evidence is offered that muscle repair takes place by the growth of fibrous connective tissue.

*Physiologic Studies of Muscles.*—Maison and Broecker<sup>806</sup> have investigated the effect of muscle training on the increased capacity to perform voluntary work after daily use. They have studied the effect of removing the blood supply to a muscle on its muscle-training characteristics. An ergograph was attached to the middle phalanges of the middle and ring fingers so that the work of the extensor digitorum communis muscle could be accurately measured. A sphygmomanometer cuff was used to produce ischemia. The contralateral muscle work was measured with its blood supply intact as a control. The muscles were voluntarily worked to fatigue once each day.

Training patterns without blood supply showed small and slow gains in total work done. The work ability of muscle working without blood supply was not significantly increased by effective training with blood supply.

The authors conclude that muscle training is largely a phenomenon of improvement in nervous direction and vascular supply.

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805. Hoff, H. E.; Winkler, A. W., and Smith, P. K.: Recovery of Fatigued Muscle Following Intravenous Injection of Potassium Chloride, *Am. J. Physiol.* **131**:615-618 (Jan.) 1941.

806. Maison, G. L., and Broecker, A. G.: Training in Human Muscles Working With and Without Blood Supply. *Am. J. Physiol.* **132**:390-404 (March) 1941.

Simonson and Enzer<sup>807</sup> have studied the efficiency of lifting loads, interrupted by short rest pauses during which the subject was standing and was seated. Two subjects were studied; they were required to lift dumbbells of 4 to 6 Kg. a vertical distance of 1 meter with straight arms. Different variations of duration of each lifting and lowering with and without pauses between each lift were studied. The authors observed that the efficiency of muscular work was increased when the work was interrupted by regular and short pauses of one minute duration. This increase was still more pronounced if the subjects were allowed to sit during the interruptions. Similar results were obtained in 2 subjects at three different speeds and with two different loads.

*Cartilage Growth and Metabolism.*—The review of the literature for the year 1941 relative to cartilage, its growth, metabolism, respiration and regeneration reveals both clinical and experimental data. One of the more popular phases, as in years past, has been the cartilage graft, and several new points are brought to light regarding technical points in its use.

Dupertuis<sup>808</sup> presents a rather complete review of the literature on the subject of cartilage transplantation with divisions into experimental studies on fresh cartilage grafts in animals and experiments with preserved cartilage. Since he found no reports on actual growth in grafts, he set out to study this himself. His observations were as follows:

1. Autografts of young ear cartilage increased in length and surface area.
2. Isografts of young ear cartilage increased in size also, but to a lesser degree.
3. Isotransplants of adult ear cartilage into young rabbits showed no growth of the graft and were surrounded by scar tissue but did not decrease in size.
4. Autotransplants and isotransplants of rib cartilage into young rabbits increased in size in their transplanted sites but grew at a slower rate than ear cartilage; the autotransplant showed a greater increase in size than did the isotransplant.
5. Autotransplants and isotransplants of preserved young rib and ear cartilage in young animals all showed gross reduction in size with varying amounts of absorption: preserved cartilage grafts were entirely unsatisfactory.

807. Simonson, E., and Enzer, N.: Effect of Short Rest Pauses in Standing and Sitting Position on Efficiency of Muscular Work. *J. Indust. Hyg. & Toxicol.* **23**: 106-111 (March) 1941.

808. Dupertuis, S. M.: Actual Growth of Young Cartilage Transplants in Rabbits: Experimental Studies. *Arch. Surg.* **43**:32-63 (July) 1941.

Young<sup>800</sup> reviews briefly the clinical and the experimental evidence regarding cartilage transplants of living and dead autogenous and homogeneous types. An experiment is reported in which 10 dogs were used. Autogenous living cartilage from the costal margins was transplanted into the abdominal wall. Half of these transplants had intact perichondrium, and the other half had the perichondrium removed. The grafts were examined grossly and microscopically over a period of two weeks to one and one-half years. The conclusion reached is that living autogenous cartilage grafts remain viable but do not change essentially their shape and size.

New and Erich<sup>810</sup> point out that freshly removed costal cartilage undergoes distortion by warping. This is most objectionable from the viewpoint of plastic operations. Preserved cartilage retains its shape because it has undergone the process of fixation. The statement is made that cartilage can be successfully transplanted from one person to another and that it may be preserved for an indefinite period in aqueous antiseptic solutions maintained at ice box temperatures. This permits the utilization of cartilage obtained post mortem. However, the authors prefer to use fresh autogenous cartilage.

Rosenthal, Bowie and Wagoner<sup>811</sup> present a complete report concerning the technical details of a method of study of the glycolytic activity of cells of bovine articular cartilage and the respiration of these cells. The material consisted of bovine articular cartilage obtained within one-half hour after slaughtering. The age of the animals ranged from 6 weeks to 11 years.

The authors' conclusions are as follows:

1. The cell count of bovine articular cartilage decreases by 75 per cent from infancy to old age.
2. The velocity of glycolysis remains proportional to the cell content of the tissue in all ages studied; thus the glycolytic power of the cartilage cells is not affected by aging.
3. The velocity of the oxygen consumption diminishes more rapidly than the cell content of the tissue; the respiratory power of adult cartilage cells is 30 per cent lower, and that of old cartilage cells is 60 per cent lower than that of young cells.

*Joints Studied from the Physiologic and Histologic Points of View.*—Little of value has been brought out in 1941 relating to the study of joints from the physiologic and histologic points of view.

809. Young, F.: Autogenous Cartilage Grafts: Experimental Study, *Surgery* 10:7-20 (July) 1941.

810. New, G. B., and Erich, J. B.: Method to Prevent Fresh Costal Cartilage Grafts from Warping, *Am. J. Surg.* 54:435-438 (Nov.) 1941.

811. Rosenthal, O.; Bowie, M. A., and Wagoner, G.: Studies in Metabolism of Articular Cartilage, Respiration and Glycolysis of Cartilage in Relation to Its

Zeller, Bywaters and Bauer<sup>812</sup> have found that thiocyanate ions and dextrose diffuse readily into joint spaces of calves following intravenous injections. They used only 6 joints for their determinations of thiocyanate and only 2 joints for determinations of dextrose. Comparisons were made between other body fluids, but no significant conclusions were drawn.

King<sup>813</sup> finds that in Charcot's joints in addition to retrogressive changes there are well developed and easily recognizable progressive and proliferative changes in the synovial membrane. The author feels that the synovial fluid should be regarded as a fluid tissue rather than a secretion of the lining cells because: (1) it contains cells which are morphologically normal; (2) changes occur in the fluid which are most readily explained on the assumption that the fluid is under the definite cellular controls, and (3) in abnormal conditions, especially if the tissues are active, the synovial membrane may be shown to merge into the fluid.

Herrmann and Ruff<sup>814</sup> present an interesting differential diagnostic criterion between inflammatory and noninflammatory effusion in the joint. They found the tryptophan values varying from 23 to 333 mg. per hundred cubic centimeters. The lowest figures were found in cases of joint transudation of noninflammatory nature, particularly in those in which the condition was due to circulatory disturbances. Traumatic effusion due to various lesions showed a value between 40 and 88 mg. per hundred cubic centimeters. In cases of tabes the values were consistently around 68 mg. per hundred cubic centimeters with normal sedimentation time. Higher values were found in cases of syphilitic effusion (95 mg. per hundred cubic centimeters), in cases of effusion from intra-articular injection (111 mg. per hundred cubic centimeters) and in cases of syphilitic arthritis (119 mg. per hundred cubic centimeters). Tuberculosis showed a value between 131 and 178 mg. per hundred cubic centimeters. The highest figures were obtained in cases of infectious arthritis (100 to 333 mg. per hundred cubic centimeters). In all cases in which the tryptophan content exceeded 95 mg. per hundred cubic centimeters, the sedimentation rate was abnormally accelerated. The diagnostic value of the test lies especially in differentiating between active tuberculosis and traumatic conditions.

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812. Zeller, J. W.; Bywaters, E. G. L., and Bauer, W.: Passage of Thiocyanate and Glucose from Blood Stream into Joint Spaces, *Am. J. Physiol.* **132**:150-156 (Feb.) 1941.

813. King, E. S. J.: Synovial Membrane in Charcot's Joint, with Special Reference to Golgi Apparatus and Synovial Fluid, *Arch. Path.* **31**:693-701 (June) 1941.

814. Herrmann, H., and Ruff, W.: Determination of Amount of Tryptophan in Effusions as New Method for Their Differentiation. *Wien. Arch. f. inn. Med.* **34**:41-56, 1940.

*Tendon and Muscle Repair.*—In the literature of the past year relating to the mechanism and the rate of tendon repair several controversial points have been discussed. The source of granulation tissue necessary for this repair, the origin of tendon cells and the nature of these cells are treated. The mechanism of scar formation and its tensile strength are dealt with in another article.

Howard<sup>815</sup> has carried out a rather careful microscopic study of the tendons of human beings, mice and rats. The tendon cells are said to lie apposed in parallel rows with oval nuclei. These tendon cells lie between the closely packed parallel collagen fibrils and on close examination can be seen to enclose or line tiny canaliculi or longitudinal spaces. These tendon cells take the neutral red and show the characteristics of endothelial cells. One can refute the view held by some investigators in the past that they are the nuclei of a continuation of the muscle sarcolemmic sheath; the fact that they line spaces suggests that they are endothelial in origin.

Howard believes tendons heal primarily by granulation tissue derived from the surrounding paratenon structures and organized blood. These tendon cells as a specific type do not reform the tendon, but the developing scar tissue under stress lines up the developing collagen fibrils into parallel bundles.

Mason and Allen<sup>816</sup> have tested the return of tensile strength in dog tendons. The tendons were cut and immediately repaired by a special technic. The experiments were divided into two groups; in one the extremities were partially or completely immobilized, and in the other unrestricted motion was permitted. They find that three tissues take part in tendon repair, namely, the tendon itself, connective tissue in and on the surface of the tendon and the connective tissue surrounding the tendon.

The first stage in repair is the formation of a fibroblastic cuff about the injured area. This is completed about the fourteenth day. Organizing differentiation then begins. The intervening tissue assumes the strength and the appearance of tendon regardless of where its origin may have been. There are two phases of increase in tensile strength during the healing process of the injured tendon. The first phase lasts from the fifth to the sixteenth day, and the second phase begins from the nineteenth to the twenty-first day and continues for an undetermined period. Restricted use of the tendon after about the fourteenth day may

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815. Howard, N. J.: Pathological Changes Induced in Tendons Through Trauma and Their Accompanying Clinical Phenomena, *Am. J. Surg.* **51**:689-701 (March) 1941.

816. Mason, M. L., and Allen, H. S.: Rate of Healing of Tendons: Experimental Study of Tensile Strength, *Ann. Surg.* **113**:424-459 (March) 1941.

be expected to lead to an increase in the tensile strength of the union for the next one or two weeks.

A series of 72 experiments on dogs and rats was performed by Chouke and Whitehead<sup>817</sup> in an effort to find the characteristics of the healing which takes place when a muscle is severed and then sutured and also when fascia is severed and then sutured. The authors have found that healing of severed striated muscle of dogs and rats occurs by fibrous connective tissue growth from the epimysium, the perimysium and the endomysium and not through regeneration of muscle cells. Fascia unites readily to fascia when closely approximated by connective tissue growth. The type of suture material employed (silk or catgut) does not appear to influence the degree or the extent of union between fascia and muscle. The union of muscle to muscle and fascia to fascia is complete in eight to eleven days after suture.

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817. Chouke, K. S., and Whitehead, R. W.: Wound Healing, with Especial Reference to Muscle and Fascia Repair, *Surgery* 9:194-197 (Feb.) 1941.

# REVIEW OF UROLOGIC SURGERY

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*(Concluded from Page 1044)*

## BLADDER

*Tumor.*—McDonald, Doss and Thompson<sup>30</sup> feel that the diagnosis of sarcoma of the urinary bladder should be arrived at cautiously because of the possibility that a neoplasm of epithelial origin may be masquerading as one of mesodermal origin. They studied tumorous tissue obtained in 9 cases in which the diagnosis of sarcoma of the urinary bladder had been made, either with or without the coincidental presence of carcinoma, and were able to demonstrate the epithelial origin of all 9 tumors. McDonald, Doss and Thompson also were able to show that the carcinoma cells had assumed characteristics which, if examined histologically, were diagnostic of sarcoma. The short clinical history and poor results (all patients died of the disease, and only 1 lived longer than a year after the neoplasm had been first recognized) attest to the extremely malignant nature of all lesions of this type in the urinary bladder.

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30. McDonald, J. R.; Doss, A. K., and Thompson, G. J.: Carcinoma of the Urinary Bladder Imitating Sarcoma, *J. Urol.* 46:38-51 (July) 1941.

Herbst<sup>31</sup> reports on 124 patients suffering from carcinoma of the bladder seen at the Surgical Clinic in Vienna. In 64 cases necropsy was done. Most of the patients were seen in the late stages of the disease, about six months after the onset of symptoms. There was no connection between the size or the situation of the tumor and the duration of symptoms. Herbst believes that tumors situated in the trigone do not cause symptoms any earlier than do tumors found in other parts of the bladder.

Herbst discusses two types of carcinoma: the ulcer and the solid protruding tumor. In an occasional case a tumor of the bladder may be the result of metastasis from a neoplasm situated in other organs. Herbst reports having seen 1 patient who had a tumor of the bladder which was secondary to a tumor of the lung and 1 who had a tumor of the bladder which was secondary to a tumor of the gallbladder.

Results of treatment of this series of patients were bad. Therapy with radium and roentgen rays offered little. In Herbst's cases, partial resection of the bladder permitted cure in 10 to 20 per cent of the cases.

Baker and Brewer<sup>32</sup> report a case of endometriosis of the bladder. The patient was a woman 33 years old who had frequency of urination for four years. Cystoscopic examination revealed a circumscribed red lesion on the left posterior wall of the bladder. Later, she had stabbing suprapubic pain in addition to frequency of urination. This pain was cyclic, occurring every two or three weeks, and was accompanied by "drawing" pains in the breast. On pelvic examination a tender mass was found associated with the wall of the bladder and separate from the cervical stump. Several months later cystoscopic examination showed a puckering in the region of the bladder. At operation a mass was found and removed from the wall of the bladder. Microscopic examination disclosed endometriosis.

Müller<sup>33</sup> reports a case in which a tumor of the bladder developed in a worker in the aniline dye industry. A small papilloma extended up into the left ureter, causing obstruction, pronounced hematuria and complete destruction of the kidney. Müller, who has had varied experience in the treatment of tumors among workers with aniline dyes, discusses the different theories concerning the occurrence of these tumors.

31. Herbst, R.: Zur Klinik und Therapie des Blasenkarzinoms, *Ztschr. f. Urol.* **34**:361-389, 1940.

32. Baker, W. J., and Brewer, J. I.: Endometriosis of the Urinary Bladder: Report of a Case, *Tr. Am. A. Genito-Urin. Surgeons* **34**:135-143, 1941.

33. Müller, A.: Bemerkungen zur Pathogenese der Anilintumoren. Mitteilung eines Falles von Ureterpapillom nach Benzidinschädigung, *Schweiz. med. Wchnschr.* **70**:232-233 (March 16) 1940.



Segal and Fink<sup>34</sup> report a case in which a cavernous hemangioma occurred in the bladder of a boy of 15 years. Cystoscopic examination revealed a mass the size of a small plum on the posterior wall of the bladder. Partial cystectomy was carried out, and histologic examination showed the tumor to be a cavernous hemangioma.

Segal and Fink state that about 40 cases of this condition have been reported. In 14 of these the patients were less than 20 years of age. Many surgical procedures have been employed, such as fulguration, local excision or radical resection by the open operation. Cures were described in 22 instances, with periods of postoperative observation ranging from several months to five years. Recurrence was noted in 4 of the reports of cases.

Conway and Broders<sup>35</sup> report a study of submucous extension of squamous cell epithelioma of the urinary bladder. A series of more than 400 specimens of tumor of the bladder removed surgically and 150 specimens of tumor of the bladder removed at necropsy was inspected. Forty of these, which when measured in the fixed contracted state presented a margin of 1 cm. or more of tissue apparently free of tumor on from one to four sides of the primary neoplasm, were chosen for study. When possible, each specimen was sectioned for microscopic study in each of four quadrants at distances of 1, 2 and 3 cm. or more from the perimeter of the primary lesion until tissue free of tumor cells was encountered or until tissue for further study was not available. Records of the patients from whom these tumors had been removed were analyzed, and the following conclusions were drawn:

It is impossible to determine how far malignant tissue extends laterally in the submucosa of the urinary bladder by gross observation at the time of operation. If segments of the bladder are to be removed at all, they should be removed only (1) when roentgen examination of the thorax reveals no abnormality which could be interpreted as metastasis, (2) when preoperative information derived from cystoscopic examination, cystography and intravenous urography indicates that the lesion is still confined to the bladder and (3) when thorough surgical exploration of the liver, the peritoneum and the regional lymph nodes reveals no abnormality which is suggestive of metastasis.

If segments of the bladder are to be removed the edges of the resected tissue should be examined microscopically before the operation is completed, to enable the surgeon to determine whether or not resection has been wide enough. If not, tissue should be removed until tissue free

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34. Segal, A. D., and Fink, H.: Cavernous Hemangioma of the Bladder, *J. Urol.* **47**:453-460 (April) 1942.

35. Conway, J. F., and Broders, A. C.: Submucous Extension of Squamous Cell Epithelioma of the Urinary Bladder, *J. Urol.* **47**:461-471 (April) 1942.

of tumor cells has been encountered on all sides of the lesion, if possible. If this is not possible, as Conway and Broders believe is frequently the case, the operation is of prognostic value only, since, because of the problem of disposition of the ureters at such a stage in the operative procedure, the ideal time for total cystectomy will have passed.

Total cystectomy, with the same reservations outlined previously for segmental resection, is the rational method of treatment from the outset for cure of epitheliomas of the higher grades, for several reasons. One is the frequency with which squamous cell epitheliomas extend widely in a lateral direction in the submucosal coat of the bladder. Another is the not uncommon finding of carcinoma in situ in a bladder which already presents a fully developed malignant lesion. Another is the modest results obtained by the present generally accepted methods of dealing with malignant lesions of the bladder, and still another is the impracticability of performing total cystectomy after the bladder has been opened with some other procedure in mind.

*Rupture.*—Brunner and Kübler,<sup>36</sup> in a report on 25 patients suffering from rupture of the bladder observed in the Surgical Clinic in Zurich, Switzerland, discuss in detail the symptoms, the diagnosis and the therapy of this condition. In 17 cases the rupture was due to blunt trauma; in 8 cases the rupture was intraperitoneal, and in 9 it was extraperitoneal. In the remaining cases, rupture in 2 was secondary to gunshot wounds; in 3 it followed instrumentation, and in 3 it resulted from blows from various tools. Cases of accidental trauma of the bladder after operative procedures were not considered. The authors said that if they are discovered at once these operative accidents rarely cause trouble.

In only 1 case of intraperitoneal rupture of the bladder was there an associated fracture of the pelvis, and in none of the cases was there associated traumatism of other abdominal organs. The prognosis which accompanies intraperitoneal rupture is better than that which accompanies extraperitoneal rupture, because of the fact that in most cases extraperitoneal rupture is associated with heavy injuries. Only 2 patients suffering from extraperitoneal rupture were saved by operation. Introduction of catheters, use of lavage of the bladder, cystoscopy and urography are unreliable and misleading; accurate estimation of the output of urine and of the value for nitrogen in blood urea usually provides diagnostic aid. An increase in the value for nitrogen in blood urea suggests resorption of urine. When patients

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36. Brunner, W., and Kübler, H.: Unsere Erfahrungen und Ergebnisse bei traumatischen Rupturen der Harnblase, Schweiz. med. Wchnschr. 70:928-932 (Sept. 28) 1940.

who have this type of rupture are seen late the danger of infection is less than the danger arising from uremia by resorption.

Lipow and Vogel<sup>37</sup> report a case of spontaneous rupture of the bladder. They state that extraperitoneal rupture of the bladder usually is associated with trauma, inasmuch as the bladder is fairly well protected by fascial coverings and bony structure, whereas intraperitoneal rupture often is not associated with trauma. The bladder usually ruptures at a previously ulcerated portion or through a wall that has been long subjected to pressure from urinary obstruction. In the cases reviewed the amount of urine found in the abdominal cavity varied from 2,500 to 4,000 cc. In Lipow and Vogel's case more than 6,000 cc. was removed.

Causative factors concerned in rupture of the bladder are numerous. Generally speaking, the pathologic processes known to affect the bladder itself and its contiguous structures are the most ordinary agents in the production of rupture. Stricture, both organic and spasmodic, is one of the most common causes. Drunkenness was a feature in 7 cases. Tumors of the bladder or in the wall of the bladder and of the neighboring structures predispose to rupture. This is also true of prostatic hypertrophy. Tuberculosis of the urogenital system, particularly of the wall of the bladder itself, and generalized systemic tuberculosis have been reported and believed to form an important causative factor. Childbearing, interference with the nerve supply of the wall of the bladder and actual fatty degeneration all have been presumed to be of some etiologic significance.

In case of intraperitoneal rupture there is usually sudden severe abdominal pain, which the patient may not be able to localize in any particular part of the abdomen. This pain usually will be described as a sensation of "something having given way." The patient when first seen may be in a state of shock which varies from mild to severe, depending on the time that has elapsed from the beginning of his symptoms. The abdomen is distended, rigid and tender, and a fluid wave is present. There is a definite sensation of fulness in the flanks. Injection of a radiopaque substance into the bladder may disclose a rent of the organ. In rupture of viscera other than the bladder active motion of the patient is attended by severe pain and discomfort, owing to the fact that the highly irritating contents of the viscus have caused acute peritonitis.

*Ulcer.*—Suter<sup>38</sup> reports a series of 11 cases of encrusted ulcer of the bladder. Five of these cases were reported in detail. All the

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37. Lipow, E. G., and Vogel, J.: Spontaneous Rupture of the Bladder, *J. Urol.* 47:277-282 (March) 1942.

38. Suter, F.: Ueber das Ulcus incrustatum vesicae, *Schweiz. med. Wchnschr.* 71:1326-1329 (Oct. 25) 1941.

patients gave a history of trauma to the bladder, either mechanical or due to infection. There was usually a superimposed infection caused by some urea-splitting organism. Surgical treatment was used in all cases. Resection of the diseased portion, followed by fulguration, usually was done.

*Interstitial Cystitis.*—Pool and Crenshaw<sup>39</sup> report on the use of a solution of silver nitrate in the treatment of 34 patients who had interstitial cystitis. All the patients, excepting those concerning whom the diagnosis of interstitial cystitis had not been definite, responded to the treatment. The method of treatment used was to begin with a very dilute solution (1:5,000) and to increase the strength daily until a solution of 1 per cent was reached. The patient's bladder was thoroughly lavaged with the solution, and then 2 fluidounces (59 cc.) of it was allowed to remain in the bladder for five minutes. At the end of this time the bladder was emptied by means of a catheter. Although Pool and Crenshaw do not claim to have cured the patients, they do say that at the time of their report some patients had been free of symptoms for as long as six months.

*Fibrosis of Vesical Neck.*—Fister<sup>40</sup> reports a case in which submucous calcification of the vesical neck occurred in a boy 13 years old. He emphasizes the importance of the fact that although the patient had neurogenic incontinence there were neither roentgen evidences nor physical observations to indicate that any large amount of residual urine was present until calcification developed with obstruction of the vesical neck. The calcification was an acquired condition and developed during the time the patient was between the ages of 8 and 13 years. Fister states that fibrosis of the vesical sac was a progressive disease which preceded calcification. Fibrosis did not appear to have been incidental to muscular hypertrophy, since there was no hypertrophy of the trigone, the wall of the bladder or the internal vesical sphincter muscle. It may have been initiated by a disturbance of innervation of the sphincter muscle, followed by an acquired infection.

The patient had gained control of the bowels at the age of 7 years, and Fister expresses the belief that if fibrosis with calcification of the vesical neck had not occurred he most likely would have gained some control of the bladder without the aid of surgical intervention.

In the tissue removed from the orifice of the bladder was a dense proliferation of fibrous tissue with degeneration of muscle and connective tissue and deposits of calcium in the submucosa. Fister is of

39. Pool, T. L., and Crenshaw, J. L.: Treatment of Interstitial Cystitis with Silver Nitrate, Proc. Staff Meet., Mayo Clin. 16:718-720 (Nov. 5) 1941.

40. Fister, G. M.: Fibrosis and Submucous Calcification of the Vesical Neck, J. A. M. A. 118:604-608 (Feb. 21) 1942.

the opinion that calcification of the submucosa suggests some similarity to the calcification which occurs in Mönckeberg's disease of the blood vessels, in which atrophy of the muscle elements and deposition of calcium occur.

Similar calcification also is found in tissues affected by tuberculosis that have undergone fatty degeneration, but Fister's patient displayed neither clinical nor pathologic evidence of tuberculosis. It is Fister's belief that the submucous calcification also suggested some similarity to so-called exogenous prostatic calculi. But the patient's prostate gland was immature, and in the section of tissue removed from the vesical neck no calcification could be seen in the prostatic tissue. There was found no suggestion of a diverticulum of the prostatic urethra in which the stones might have developed. Disease of the parathyroid glands as a causative factor in the calcification was considered, but there was no clinical evidence that such a disturbance was present.

*Prolapse.*—Macpherson<sup>41</sup> reports a case of ureterocele in which prolapse through the external urinary meatus of a woman had occurred. When the labia were separated a bright red tumor was seen projecting through and beyond the external urethral orifice. It had an appearance which was suggestive of a polyp. When distended with urine, it was 2 inches (5 cm.) long and 1 inch (2.5 cm.) in diameter but could be extruded farther by traction. Reduction was simple; first, the sac was emptied and then pressed upward and backward against the external urethral orifice. The ureterocele then slipped back and as it did imparted much the same sensation as that which the physician notices in the reduction of a hernia. When the patient strained, the ureterocele could be prolapsed at will outside the external urinary meatus.

At operation the patient was asked to micturate. As she complied, the ureterocele presented outside the external urinary meatus. A fine ureteral catheter was then inserted into the ureteral orifice and cut down on for a distance of 1½ inch (roughly, 4 cm.) with an electrode. The diathermy cutting current was utilized, and the cyst was laid open. A finger was then inserted into the wound in the ureterocele, as a physician would insert a finger into a hernial sac to put it on the stretch, so to speak, and a circular section of tissue was excised. A week later cystoscopic examination disclosed that the inflated wall of the ureterocele had completely collapsed. Through a central opening, corresponding to the portion excised at operation, the dilated lower end of the ureter could be seen at the point at which it entered the bladder. The redundant wall of the ureterocele arose circularly around the ureteral orifice and was thrown into fairly firm, puckered folds. At this time

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41. Macpherson, I.: Ureterocele, with Prolapse Through the External Urinary Meatus, *Brit. J. Surg.* 29:294-298 (Jan.) 1942.

a right-sided ureterocele was found, which until then had been completely obscured by the one first seen, on the opposite side. The ureteral orifice was not visible. At the second operation, a diathermy electrode was passed through the cystoscope and the wall of the ureterocele on the right was split in a vertical direction by the cutting current throughout its whole length. Later, cystoscopic examination revealed both ureteral orifices. The left one was situated near the center of a slightly elevated circular portion of healthy mucosa. The right one could be seen at the base of a hoodlike projection of elevated translucent mucosa which had been slit vertically and had not contracted. There was no obstruction of either ureteral orifice, and the neighboring vesical mucosa presented a normal appearance. On the basis of the mode of onset and the disappearance of the symptoms in this case, Macpherson believes that a moderately large ureterocele can be present without causing any symptoms. The symptoms of his patients began suddenly and progressed without remission, and the onset of them seemed to date from the time the ureterocele on the left became large enough to reach the internal meatus and to cause obstruction to micturition. All symptoms were relieved by removal of the obstruction in the left ureter. Macpherson suggested that in this case the ureterocele did not represent prolapse of the lower end of the ureter as a whole, but prolapse and ballooning of only the mucous lining of the ureter.

#### PROSTATE GLAND

*Hypertrophy.*—Emmett<sup>42</sup> is of the impression that many patients suffering from the "tabetic type" of cord bladder can be helped by transurethral resection of the vesical neck. He reports a case to illustrate his view. The patient was a man 66 years of age who had found it necessary to wear a urinal bag for fifteen years and in whom complete urinary obstruction had developed, requiring catheterization three weeks before his admission to the hospital. Although only 8 Gm. of tissue was removed, the patient was able to void a normal stream of urine, to empty his bladder completely and to go through the night with only an occasional rising to void. Emmett believes that a bladder weakened by distention resulting from impairment of the sensory nerves which supply the bladder is more easily obstructed than is a normal bladder.

Kretschmer<sup>43</sup> discusses the end results of removal of obstruction of the neck of the bladder on the basis of study of the presence or the

42. Emmett, J. L.: Urinary Incontinence of Fifteen Years' Duration in a Tabetic Patient Relieved by Transurethral Resection: Report of a Case, Proc. Staff Meet., Mayo Clin. 16:728-730 (Nov. 12) 1941.

43. Kretschmer, H. L.: End Results in Removal of Bladder Neck Obstruction, J. A. M. A. 119:336-337 (May 23) 1942.

absence of residual urine in 144 cases in which prostatic resection had been done. This study revealed several interesting facts:

1. A definite increase in the percentage of patients who had no residual urine was noted; that is, this percentage increased from 66.3 in the first series to 78.47 in the third series of cases studied.

2. There was a reduction in the percentage of those patients who had 11 to 20 cc. of residual urine. This percentage was reduced from 16.11 in the first series to 13.88 in the third series.

3. A definite increase in the sum total of these two groups was recorded; that is to say, this sum total was 82.41 per cent in the first series, 87.90 per cent in the second series and 92.36 per cent in the third series.

4. There was a pronounced reduction in the percentage of patients who had from 21 to 30 cc. of residual urine. This percentage was 6.22 in the first series, 6.95 in the second series and 2.77 in the third series.

5. A decided reduction in the percentage of patients who had from 31 to 40 cc. of residual urine occurred; it decreased from 1.83 in the first series to 0.694 in this series.

6. There was a reduction in percentage of patients who had 41 to 50 cc. of residual urine, namely, from 2.19 to 0.694.

7. A definite reduction in the percentage of patients who had more than 50 cc. of residual urine was noted; it decreased from 7.32 in the first series to 3.47 in the final series.

Lich <sup>44</sup> investigated renal dysfunction in cases of prostatic obstruction by the use of simultaneous tests of the clearance of insulin and phenol red. He states that renal dysfunction in the presence of prostatism is primarily dysfunction of the tubules. The disturbed renal function in prostatism is definitely improved by continuous vesical drainage. Renal damage caused by prostatism is partially reversible, he states. Reestablishment of renal function is not complete, but reaches a peak beyond which no further functional improvement occurs.

*Carcinoma.*—Thompson <sup>45</sup> says that carcinoma of the prostate gland which has developed sufficiently to cause urinary obstruction cannot be completely eradicated by a surgical procedure, because it has already spread through the perineural lymphatic vessels. He believes that adequate transurethral resection, with removal of all the obstructing

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44. Lich, R., Jr.: Renal Dysfunction in Prostatism, Surg., Gynec. & Obst. **74**:475-478 (Feb. 16) 1942.

45. Thompson, G. J.: Carcinoma of the Prostate: Its Conservative Surgical Treatment, South. Surgeon **10**:271-278 (April) 1941.

tissue, and the subsequent employment of high voltage roentgen therapy offer the patient the best prognosis. He also believes that the almost negligible risk of the operation (less than 1 per cent in 253 cases) and the almost certain assurance of perfect control of micturition post-operatively are strong arguments in favor of transurethral resection.

Barringer<sup>46</sup> states that authenticated five year cures of prostatic carcinoma are rare. He thinks that so-called aspiration biopsy is a valuable means by which to make an early diagnosis in about 50 per cent of the cases.

At Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, according to Barringer, there have been two general lines of treatment: (1) radiation therapy with radon needles or seeds applied perineally or suprapubically and (2) minimization of operative intervention. Of 352 patients, 36 (10 per cent) lived for more than five years. Of these 36, 15 died of carcinoma between the fifth and the tenth year, so that there remained 21, or 6 per cent, apparently free of carcinoma for periods of between five and nineteen years. High voltage roentgen therapy has been of little use in control of this disease. Radiation treatment is of great value in maintenance of patency of the urethra, he says, and in enabling a patient to empty his bladder throughout the years of life remaining to him. This applies to the small carcinomas confined to the prostatic and immediate periprostatic areas. Castration carried out by either surgical operation or roentgen rays may prove a factor in control of this disease. It should not be used to the exclusion of other methods.

*Tuberculosis.*—Strom and Thompson<sup>47</sup> report a case in which a patient came to necropsy. They believe the disease present represented true primary prostatic tuberculosis of the genital tract. Routine gross and microscopic examination did not reveal any evidence of tuberculosis elsewhere in the body. A small purulent abscess 4 mm. in diameter was found in the left lateral lobe of the prostate gland. This abscess had the typical histologic structure of tissue affected by tuberculosis and contained acid-fast organisms. Microscopic sections of the posterior urethra, the seminal vesicles, the vasa, the epididymes and the testes exhibited no pathologic changes. Strom and Thompson are certain that the prostate gland contained the only tuberculous lesion in the genital tract and possibly in the patient's entire body. This case was said to constitute further evidence against the old teaching that genital tuberculosis in the male subject always is initiated in the epididymes.

46. Barringer, B. S.: Prostatic Carcinoma, *J. Urol.* 47:306-310 (March) 1942.

47. Strom, G. W., and Thompson, G. J.: Primary Tuberculosis of the Prostate: Report of Case, *J. Urol.* 45:858-862 (June) 1941.



## TESTICLE, EPIDIDYMIS AND VAS DEFERENS

*Tumor of Testicle.*—Adams<sup>48</sup> reviews 21 cases of malignant testicular neoplasm from a pathologic standpoint. Study of this material lends support, he thinks, to the theory that these tumors, including seminomas and chorionepitheliomas, probably have a common origin. It has been held that they arise from a spermatogenic cell or cells. Such cells may be pluripotential and give rise to tridermal metastasis. A case in which there were single tridermal metastatic processes, each process containing derivatives of all three germ layers, was cited as evidence for such occurrence. Adams suggested that trophoblastic tissue is present in teratoma testis more often than is commonly supposed and that its presence accounts for the appearance of large amounts of gonadotropic hormone in the urine of patients who have such tumors. The occurrence of hypertension in association with the excretion of large amounts of gonadotropic hormone in the urine was noted.

Hamilton and Gilbert<sup>49</sup> state that among men who have one testicular cancer, the likelihood of the development of cancer in the second testis is from several hundred to several thousand times greater than would be expected on the basis of chance association. Abdominally retained testes are especially susceptible to bilateral cancer. One of every 8 men who had bilateral testicular cancer also had abdominally retained testes, the authors state, a condition which can be estimated to occur in probably much less than 0.005 per cent of men. The pronounced carcinogenic tendency of abdominal testes also can be ascertained differently. Hamilton and Gilbert say that although the incidence of cancer in the presence of inguinal testes is high, the occurrence of cancer in abdominal testes is some fifty times higher, as is seen by comparison with the ratio of abdominal and inguinal testes to uncomplicated cryptorchidism. The authors say that bilateral tumors occur predominantly in the reproductive years of life, but they remark that the first tumor in such cases usually occurs later in life than does the unilateral tumor. The greatest number of both unilateral and bilateral tumors, and especially those occurring during the reproductive years, are unicellular types.

The relative percentages of the various types of tumors are the same for bilateral as for unilateral cancer, save for the fact that chorionepitheliomas are not found bilaterally. Hamilton and Gilbert advance additional evidence to the effect that prenatal factors are significant in

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48. Adams, J. E.: A Study of Malignant Testicular Tumors Including Case Reports of Chorionepithelioma Accompanied by Hypertension and Teratoma Testis with Single Tridermal Metastases, *J. Urol.* 47:491-507 (April) 1942.

49. Hamilton, J. B., and Gilbert, J. B.: Studies in Malignant Tumors of the Testis: IV. Bilateral Testicular Cancer; Incidence, Nature and Bearing upon Management of the Patient with a Single Testicular Cancer, *Cancer Research* 2:125-129 (Feb.) 1942.

a patient's predisposition to testicular cancer. It is possible, they believe, that estrogens may play a role in the instigation of cryptorchidism and that gonadotropins may operate in the stimulation to carcinogenesis during the patient's so-called reproductive years of life. They say that management of the patient who has cancer of one testis must be concerned with the possibility that primary involvement of the other testis may occur. Despite the usually rapidly fatal course of the patient who has testicular cancer, a tumor has appeared in the other testis of 15 per cent of those who had inguinal testes and in the other testis of 30 per cent of those who had abdominal testes. The second testis of a man suffering from bilateral cryptorchidism and cancer of one testis must be viewed as a site of potential carcinogenesis.

Hamm<sup>50</sup> reports a case in which a Wilms tumor afflicted a 64 year old man. The patient complained chiefly of hematuria. Cystoscopic examination showed that bloody urine was coming from the right, and that clear urine emerged from the left, ureteral orifice. The pyelogram of the left kidney was normal; that of the right kidney showed some obstruction characteristic of renal tumor. The right kidney was removed, and histologic examination revealed a mixed tumor containing carcinomatous and sarcomatous structures.

Graves and Lawrence<sup>51</sup> discuss bilateral embryonal carcinoma of the testicle and report a case. Their patient was a man 33 years old who had noticed that a slight enlargement of the right testicle had been present for two years. Orchidectomy was refused. At about this time the left testicle started to enlarge. On examination, a mass in the lower part of the abdomen was found. The left testicle was removed first; later the right one was excised. The diagnosis was embryonal carcinoma of the testicle. Roentgen therapy was also administered. Ten months later the patient reported that he had lost 5 pounds (2.3 Kg.). He complained of nothing else and was working.

Graves and Lawrence state that they favor external irradiation rather than surgical intervention as the primary form of therapy in the treatment of such patients, whether they do or do not have metastasis. Orchidectomy is performed in such a program when the full effect of irradiation has been obtained in the testicle and when the local reaction in the scrotum has subsided. In all their cases, regardless of whether the primary tumor is removed or irradiated and whether demonstrable metastasis is present or not, a full series of treatment with roentgen rays is always administered and is always understood to include treatment

50. Hamm, F. C.: Wilms' Tumor in a Sixty-Four Year Old Male: Report of a Case, *J. Urol.* **47**:403-409 (April) 1942.

51. Graves, R. C., and Lawrence, K. B.: Bilateral Embryonal Carcinoma of the Testicle with a Note on the Technique of Orchidectomy for Malignant Disease, *Tr. Am. A. Genito-Urin. Surgeons* **34**:227-236, 1941.

by maximal dosage through both the anterior and the posterior portals of all the lymph gland-bearing regions *on each side*, from the pelvis to the diaphragm. The thorax is not treated unless there is roentgenologic evidence of involvement in this region or unless palpable supraclavicular lymph nodes are present. Under such circumstances the thorax and the neck are included in the roentgen treatment. Graves and Lawrence say that surgical dissection of retroperitoneal glands should be reserved for those unusual and desperate instances in which the malignant tumor is of a type resistant to radiation, as evidenced by its response to treatment or by the pathologic report, if the testicle has been removed.

Graves and Lawrence say that they have been making some exceptions to the rule that irradiation should be carried out first. In early stages of tumors, when only slight changes can be felt in the involved testicle and when the presence of a neoplasm can be suspected only, they think that prompt and early diagnosis cannot be obtained except by prompt and early orchidectomy. Graves and Lawrence emphasize the importance of careful technic in the performance of orchidectomy in the presence of malignant disease of the testicle, positive or suspected. By means of such technic the likelihood of widespread dissemination of that disease through manipulation of the tumor can be minimized. They say that no more vicious tumor occurs in the male genitourinary system, and declare that there is none which is more readily disseminated, than carcinoma of the testicle. They prefer a somewhat more radical procedure than that commonly employed. In all the examinations and preparations for operation, the scrotal contents are treated with the utmost gentleness. The inguinal canal is opened first, without inclusion of the scrotum in the incision, and it is opened high enough to permit adequate exposure of the spermatic cord at the level of the internal inguinal ring. At this level the cord is doubly ligated with as little trauma as possible and without the application of clamps. It is then divided between the ligatures with the cautery or cutting current. At this stage the incision can be extended downward sufficiently to permit removal of the distal portion of the cord from its bed and to allow gentle enucleation of the testicle, with its intact tunic, from the cavity of the scrotum. Great care should be taken not to incise the tunica vaginalis or to cut into the tumor at any point. This procedure, according to Graves and Lawrence, avoids all manipulation of the malignant process until its lymphatic and vascular connections with the body have been severed.

Graves and Lawrence<sup>52</sup> report a case in which bilateral embryonal carcinoma of the testicle had afflicted a 33 year old patient. The two

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52. Graves, R. C., and Lawrence, K. B.: Bilateral Embryonal Carcinoma of the Testicle with a Note on the Technique of Orchidectomy for Malignant Disease, *J. Urol.* **47**:482-490 (April) 1942.

tumors were of large size and exhibited evidence of metastasis to retroperitoneal lymph nodes. Preliminary bilateral orchidectomy was done. Clinical disappearance of the metastatic disease followed the administration of high voltage roentgen ray therapy directed to the abdomen and pelvis. The patient was alive and without definite evidence of disease about ten months after treatment.

*Torsion of the Testicle.*—Ownby and Atkinson<sup>53</sup> state that torsion of the testicle should be more nearly accurately called "torsion of the spermatic cord." Torsion is caused by a sudden axial rotation of the testicle or testes. This causes constriction of the blood vessels of the spermatic cord and results in an acute circulatory disturbance of the testes and adnexa. In 75 per cent of cases the patients are less than 21 years old. Wallenstein is said to have found that in 144 cases the condition occurred on the right side and that in 142 cases it occurred on the left side. He also is said to have found 24 cases in which the condition occurred bilaterally. Pain—sudden, sharp and severe—is common. It usually follows some sort of muscular effort. As swelling increases pain becomes more severe. When the condition is recurrent pain may be intermittent. Unilateral edema of the scrotal skin occurs early and is sharply limited to the side on which the torsion is exerted and extends up to the site of the twist, with fixation of the skin to the underlying scrotal contents. There is retraction of the scrotal contents upward, brought about by shortening of the cord. The epididymis, if it is palpable, occupies an abnormal position in relation to the testis. In later stages, distinction between epididymis and testis is impossible. Elevation of the scrotum increases the pain; but when epididymitis is present such a procedure usually relieves the pain. The diagnosis frequently is erroneous. The most important factor is that the physician consider the possibility that torsion may be present in every case of pain and swelling in the scrotum. Possibility of the presence of torsion must be considered in every case of inguinal swelling with which pain is associated, particularly if the testicle is not palpable in the scrotum. This applies to every male from birth to old age.

Ownby and Atkinson state that to be effective treatment must be instituted early. Detorsion rarely has been successful. Although the direction of torsion usually is clockwise on the right and counterclockwise on the left, there is no certainty that these conditions will be present in any given case. As an emergency procedure, detorsion may be attempted, but such an attempt should be gentle. Even if the detorsion is successfully effected, surgical exploration of the testicle and orchidopexy or orchiectomy are indicated. When either of the procedures is

53. Ownby, J., Jr., and Atkinson, R. C.: Torsion of the Testicle, California & West. Med. 56:251-253 (April) 1942.

performed the contralateral testicle should be anchored, since the same anatomic conditions predisposing to torsion usually are present in that testicle.

*Blood Supply.*—Golder and Wildbolz<sup>54</sup> discuss the blood supply and anastomosing vessels of the testis and epididymis. They report an investigation carried out on 54 testicles that had been obtained by surgical removal or at necropsy. After initial experiments to determine the choice of the dye and the roentgenographic methods to be used, optimal results were gained by injection of a mixture of a colloidal suspension of thorium dioxide (thorotrast) and methylthionine chloride U. S. P. (methylene blue) into the arterial system; in most cases the mixture was injected into the internal spermatic artery. In cases in which conditions were favorable the whole system (internal and external spermatic artery, deferential artery and pampiniform plexus) became clearly visible in the stereoscopic roentgenogram. Golder and Wildbolz describe a number of variations of the blood supply. First, the internal spermatic artery reaches (or its main branches reach) the testicle in the middle third of its posterior aspect. The further course inside the testicle takes place in one of the following ways: (1) without further division, through the middle of the parenchyma of the testicle from the back to the front aspect, (2) by passing down the posterior aspect around the inferior globe, (3) by entrance through the tunica albuginea in two main branches, one following type 1 and the other following type 2, (4) by splitting up into several branches, penetrating on different heights on the back aspect, and (5) by division into several branches immediately after entrance through the tunica albuginea.

In a second variation of the blood supply, anastomoses of the internal spermatic artery with the deferential artery occur according to the following main types: (1) When anastomosis is external, the deferential artery connects with a branch of the internal spermatic artery over the posterior aspect of the epididymis, and (2) when anastomosis is internal, the anastomosis lies inside the tunica albuginea. Two variants are possible: (1) connection in the superior and (2) connection in the inferior testicular pole. In Bevan's operation for undescended testicle, during mobilization of the dystopic testicle it is necessary to divide the vascular plexus of the internal spermatic artery as far as possible from the testicle in order to insure eventual anastomosis with the deferential artery. In epididymectomy, the anastomosis in the region of the lower portion of the epididymis which passes to the inside

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54. Golder, O.: Die Arterien des menschlichen Hodens und Nebenhodens, ihre Anastomosen und deren Bedeutung in der Chirurgie, *Ztschr. f. urol. Chir. u. Gynäk.* **45**:406-422, 1940. Wildbolz, H.: Die Arterien des menschlichen Hodens und Nebenhodens. (Nachwort zu der Arbeit von O. Golder), *ibid.* **46**:5-6, 1941.

of the testicle must be ligated as far as possible from the testicle. Ligations eventually necessary in the tunica albuginea may lead to ligation of the internal spermatic artery and therefore to partial or total necrosis of the testicle. Golder and Wildbolz consider the results of these experiments on the blood supply to be of great value in the performance of epididymectomy. They say that in recently reviewed cases orchidectomy has been much more common than epididymectomy, even in cases of epididymitis.

There have been two objections to the performance of epididymectomy. First, in inflammatory diseases, especially in cases of tuberculosis, it was thought that the testicle also became infected early in the course of the disease and that epididymectomy was not sufficient. This has been disproved by pathologic and anatomic investigation. Second, it has been said that atrophy of the testicle occasionally results after epididymectomy. According to Golder and Wildbolz, careful surgical technic and preservation of the blood supply will prevent this.

The greatest danger to the testicle from injury to the vessels does not arise in separation of the superior globe, but in isolation of the body of the epididymis. Incision must be made very close to the epididymis in order to preserve the internal spermatic artery, which enters the posterior part of the testicle in the middle third portion. Hemostasis must be carried out carefully, because the spermatic artery and its branches sometimes adhere very closely to the testicular capsule. Ligation of the vessels must be superficial and carried out with small instruments. The same care must be taken in removal of the inferior portion of the epididymis, since in some cases there is a variation in the course of the spermatic artery, and it may enter at the lower portion of the testicle.

*Infertility.*—Charny and Meranze,<sup>55</sup> in discussing biopsy of testicular tissue in cases of male infertility, say that it is an innocuous procedure and that it should be established as a routine procedure in these cases. Failure of tubular development is indicated histologically by the presence of small tubules which are filled with undifferentiated cell forms. Peritubular fibrosis is not present. Degenerative lesions, if acute, can be recognized in biopsy of testicular tissue by the presence of necrosis and desquamation of the tubular epithelium. If the lesions are long standing, peritubular fibrosis is a distinct feature and signalizes either the end stage of an inflammatory process or the replacement fibrosis which results from shrinkage of the tubules.

The presence of peritubular fibrosis suggests severe damage to the youngest epithelial cells of the tubules, and this damage probably has

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55. Charny, C. W., and Meranze, D. R.: Testicular Biopsy: Further Studies in Male Infertility, Surg., Gynec. & Obst. 74:836-842 (April) 1942.

affected their regenerative potentialities. The administration of an estrogen or an androgen, such as diethylstilbestrol or testosterone propionate, induces tubular degeneration, both in the hypersexual male and in the patients with hypogonadism. Charny and Meranze say that the majority of male patients of relative infertility have no endocrine disturbances. Deficiencies in their semen are the results of degenerative lesions of the seminiferous tubules caused by either regional or constitutional inflammatory or toxic processes. Endocrine therapy, they declared, is not indicated in such instances.

*Tumor of Epididymis.*—Friedman and Grayzel<sup>56</sup> report a case in which tumor of the epididymis afflicted a 57 year old man. On examination the left testicle was found to be about four times normal size. The epididymis was stony hard, and the cord was thickened. Orchidectomy was done, and a diagnosis was made of "fibrous myoma of the epididymis." Friedman and Grayzel summarize data of thirteen collected cases and find that the average age of the patients was 44 years. The usual history was that of gradual increase in the size of a painless scrotal tumor. In most cases the tumor was hard, round, nodular and not tender. The treatment is epididymectomy. If the testicle is found to be involved, a frozen section should be prepared and studied histologically before complete removal of the epididymis and castration are attempted.

O'Brien<sup>57</sup> reports a case of primary sarcoma of the epididymis. He states that there are, inclusive of his report, only 92 cases recorded in the literature. The role trauma plays in the causation of tumors of the epididymis and testicle, a subject of controversy, is significant, he says. The train of events in O'Brien's case, as well as in the cases of others, justifies this opinion. In all cases of scrotal or testicular injury the patient should be kept under prolonged observation. In O'Brien's case, a fibrosarcoma developed within six months after the patient had sustained a violent blow to the scrotal region. Metastasis to bone may occur to an unpredictable degree. The usual sites of localization are the lumbar vertebrae and, to a lesser extent, one distant bone or more. In no case referred to by O'Brien was there such rapid and widespread dissemination as occurred in his own case.

*Cyst of Epididymis.*—Baird<sup>58</sup> reports a case in which a cyst of the epididymis became twisted on its pedicle. The patient was a boy of

56. Friedman, H. H., and Grayzel, D. M.: Myomatous Tumors of the Epididymis, *J. Urol.* **47**:475-481 (April) 1942.

57. O'Brien, M. G.: Primary Sarcoma of the Epididymis: Case Report, *J. Urol.* **47**:311-319 (March) 1942.

58. Baird, S. S.: Cyst of the Epididymis Twisted on Its Pedicle: Case Report with Review of the Literature, *J. Urol.* **47**:372-378 (March) 1942.

15 years who complained of pain in the left groin and also of swelling and pain in the left side of the scrotum. At operation a small intravaginal purplish cyst was found below the testis; it was joined by a short pedicle to the tail of the epididymis. The pathologic diagnosis was "benign cyst of the epididymis." Operation is the treatment of choice in similar cases of torsion of the appendages of the testis and epididymis. Baird quotes Randall's statement: "The operation is so simple, and so devoid of any serious complications, that it should always be advised. . . . The question of conservative—nonoperative—treatment is ill-advised: (1), because no local treatment relieves the distress; (2), because detorsion and recurrent attacks are possible; (3), because the nonoperative recovery can take longer than the operative removal and convalescence."

*Calcification of Vas Deferens.*—Lowsley and Riaboff<sup>59</sup> review 32 cases of calcification of the vas deferens, ampulla of the vas and seminal vesicle (31 taken from the literature and 1 case of his own). Their study reveals that this condition may occur at any age of the patient, from youth to senility. The youngest patient who had the condition was 14 years of age; the oldest was 81 years old. In 12 cases, or in more than a third, calcification had occurred after the patients had reached the age of 60 years; in 5 cases the patients were between the ages of 50 and 60 years; 3 patients were in the fourth decade; 1 was in the third decade, and 3 were in the second decade. Of the 32 cases studied, the condition was found at necropsy in 21. In 1 case it was found at operation, and in only 10 cases, including Lowsley and Riaboff's case, had the condition been diagnosed clinically in the living patient.

#### PENIS

*Plastic Induration.*—Volavsek<sup>60</sup> reports 198 cases of plastic induration of the penis from the Dermatologic Clinic of Vienna. The reaction of connective tissue to local hypertrophy is one of the most common causes of this condition, and in addition there are various irritative factors which are important, such as mechanical trauma and disturbance of circulation to the tissues. Of all the patients, 4.6 per cent had an associated digital Dupuytren's contracture. On the other hand, 34 per cent of the patients who had Dupuytren's contracture also had plastic induration of the penis. Of the patients treated with radium, 32.8 per cent progressed to complete recovery; 47 per cent were partly

59. Lowsley, O. S., and Riaboff, P. J.: Calcification of the Vasa Deferentia. *J. Urol.* 47:293-298 (March) 1942.

60. Volavsek, W.: Zur Kenntnis der Induratio penis plastica (mit bes. Berücksichtigung ihrer Beziehung zur Dupuytren'schen Kontraktur), *Ztschr. f. Urol.* 35:173-175, 1941.



healed, and the condition of the rest was not influenced. In those cases in which definite calcification or ossification had occurred, it was necessary to remove calcified tissue by surgical operation. Volavsek says that in his opinion radium provides the best results of any type of treatment.

*Phimosis.*—Hoffmann<sup>61</sup> reports a case in which complete phimosis developed after circumcision of a 4 week old baby. Urinary stasis occurred, necessitating a second operation.

*Periurethral Extravasation.*—Steller<sup>62</sup> discusses some anatomic aspects of the periurethral fasciae. He distinguishes three different layers. First, he disagrees with the descriptions of some other observers, who have reported complete involvement of the penis and scrotum by a continuous fascial layer. The first of the three layers of fascia reported by Steller is Colles' fascia, which is composed of the superficial abdominal fascia, the cremasteric fascia, the superficial perineal fascia and the penis. He states that the scrotum has no fascial layer corresponding to this complex group and remarks that this grouping of fasciae is important in the localization and spread of urinary extravasation. The second layer of fascia consists of the aponeuroses of the internal and external oblique muscles, the suspensory ligament of the penis, the external periosteal layer of the pubic bone and the external sheet of the urogenital diaphragm. The third fascial layer is composed of the fascia of the transverse abdominal muscles, the internal periosteal layer of the pubic bone and the internal sheet of the urogenital diaphragm.

In 90 per cent of cases of periurethral urinary extravasation, stricture of the urethra was found. Extravasation occurred usually just distal to the point of the lesion. Seventy-five per cent of the patients earlier had had gonorrhea. Further development of the pathologic processes, says Steller, depends on the extent of the urinary infection. Ammoniacal decomposition of the urine, which commonly is present, is said to favor an anaerobic type of infection (usually caused by *Borrelia refringens*). The spread of the extravasation is greatly increased by the movement and position of the different layers of periurethral fascia. Steller also describes three different types of spread of extravasation. In the first the infection starts from the bulbous portion of the urethra and spreads by means of the superficial fascia and the skin. This results in infiltration of the perineum, the scrotum and the inguinal and pubic regions. The prognosis is good. In the second infection occurs in the

61. Hoffmann, W.: Schwielenbildung und Verengerung des Harnröhrengangs nach Phimosenoperation, Schweiz. med. Wchnschr. **70**:142-143 (Feb. 17) 1940.

62. Steller, L.: Die periurethrale Urinifiltration und die periurethralen Faszien (eine anatomische und klinische Studie), Ztschr. f. Urol. **35**:192-204, 1941.

membranous portion of the urethra, and the infection spreads between the two sheets of the urogenital diaphragm. Later, rupture of the diaphragm occurs, either outwardly or inwardly; at times accompanied by infiltrations of the pelvic organs. The prognosis is bad. In the third infection spreads from the prostatic urethra, with infiltration of the organs of the pelvis, not uncommonly causing death of the patient. The treatment of all patients is incision of the extravasated region and drainage of the bladder; but neither is sufficient without the other.

#### THERAPY WITH SULFONAMIDE COMPOUNDS

Hendricks,<sup>63</sup> in discussing changes in the blood resulting from the administration of sulfonamide compounds, states that in 40 per cent of 433 patients who received one or more of these compounds mild to severe anemia developed. The percentage of total instances of anemia was about the same for sulfanilamide, sulfapyridine and sulfathiazole. Infants and children who received sulfanilamide or sulfapyridine were more susceptible to severe anemia than were adults. Although anemia developed among 50 per cent of infants and children who were treated with sulfathiazole, no severe or moderately severe changes occurred in any. In all age groups, severe or even moderately severe anemia occurred less frequently when sulfathiazole was administered than it did when sulfanilamide or sulfapyridine was employed.

The number and severity of the various types of anemia were not dependent on the total doses received by the patients, the duration of treatment or the concentration of the drug in the blood. Therefore Hendricks concludes that the administration of small doses for a longer period than is usual is no insurance against the development of anemia. Leukopenia developed among 2.3 per cent of patients, and in 4 cases leukopenia proceeded to agranulocytosis, with 2 deaths. Hendricks said that blood counts must be made routinely every two to three days during the entire course of treatment with any of the sulfonamide compounds. Since reactions may occur after cessation of therapy, patients should be kept under surveillance after treatment has been discontinued.

Keitzer and Campbell<sup>64</sup> report 11 cases in which renal complications appeared secondary to the administration of sulfadiazine. Complications usually appeared by the seventh day of administration of this drug. The average daily dose was 5.5 Gm. The average concentration of the drug in the blood was 11 mg. per hundred cubic centimeters. This suggests that a safe dose is 4 Gm. a day and that a safe concentration of the drug

63. Hendricks, C. B.: *Sulfonamide Compounds: Blood Changes Therefrom*. California & West. Med. **56**:253-257 (April) 1942.

64. Keitzer, W. A., and Campbell, J. A.: *Renal Complications of Sulfadiazine*, J.A.M.A. **119**:701-703 (June 27) 1942.

in the blood is one of not more than 8 mg. per hundred cubic centimeters. They believe that sulfadiazine, since it is better tolerated by the stomach, is a more dangerous drug in respect to its power to produce renal complications than are others, because physicians are more likely to be less vigilant when a drug appears to be well tolerated. Keitzer and Campbell advise the following method of treatment in any type of renal complications caused by sulfonamides:

1. Administration of the drug should be halted immediately at the first sign of hematuria, renal colic or oliguria.

2. Fluids should be forced.

3. If oliguria is present, with an output of urine of 500 cc. or more, a delay of from twelve to twenty-four hours before cystoscopic examination is undertaken, in the hope that diuresis will relieve the situation, may be tried.

4. Cystoscopy and catheterization of the ureters should be carried out immediately when oliguria persists or anuria is present.

5. The ureteral catheters should be left in place as indwelling catheters for from twenty-four to forty-eight hours, until the return flow of urine is clear.

6. Kidneys should be irrigated with a warm 2.5 per cent solution of sodium bicarbonate or with a warm isotonic solution of sodium chloride. Keitzer and Campbell have at times alkalized the patient intravenously as well as orally.

7. Retrograde pyelograms should be made prior to withdrawal of the catheters.

Huber <sup>65</sup> reports a case in which anuria occurred secondarily to the administration of sulfapyridine. Both ureters of the patient were completely filled with crystals. Ureteral catheterization was carried out, but death resulted from cardiac failure.

Cook <sup>66</sup> reports his experience with sodium sulfathiazole in the treatment of approximately 200 patients who had infection of the urinary tract. He used a dose of from 20 to 60 Gm. daily for a period of six to ten days and found that (1) gram-positive organisms were affected equally well except for members of the genus *Pseudomonas*, which were most obstinate to treatment, and that (2) gram-positive cocci, except for *Streptococcus faecalis*, all responded satisfactorily. Cook also notes that the drug exerted its effects very promptly, on account of its rapid absorption, and that its toxic effects were almost nil.

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65. Huber, W.: *Ergänzender Beitrag zur Frage der Drogenan- Komplikationen*. Schweiz. med. Wchnschr. **70**:884-885 (Sept. 14) 1940.

66. Cook, E. N.: Sodium Sulfathiazole in the Treatment of Infections of the Urinary Tract. Proc. Staff Meet., Mayo Clin. **16**:717-718 (Nov. 5) 1941.

Helmholz<sup>67</sup> is of the opinion that the ideal urinary antiseptic agent has not been found. Theoretically it should be one that would act in a urine of any reaction and one that would be excreted by the damaged kidney in a bactericidal concentration. Although it is not ideal, sulfathiazole is bactericidal for six of the most common bacteria found in infections of the urinary tract. He found that a concentration of the drug in the blood of 200 mg. per hundred cubic centimeters was sufficient for the cure of practically all infections excepting those caused by members of the genus *Pseudomonas*, which probably will require the concentration in the blood to be 300 mg. per hundred cubic centimeters. He found that the effectiveness of the drug for the various bacteria (on an ascending scale) is as follows: *Pseudomonas aeruginosa*, *Str. faecalis*, *Escherichia coli*, *Aerobacter aerogenes*, *Proteus ammoniae* and *Staphylococcus aureus*. He also noted that there was some variation in the effect of the drug at various values for  $p_H$ , and that this characteristic was particularly marked in the case of *Streptococcus faecalis*.

By experiments in vitro on the *Str. faecalis*, Helmholz<sup>68</sup> undertook to determine the efficacy of sulfathiazole in the treatment of urinary infections. For this purpose he carried on a series of experiments with urine at a  $p_H$  of 6.5, 6.0, 5.5 and 5.0, and with concentrations of 10, 20, 30, 50 and 100 mg. of the drug per hundred cubic centimeters of urine. For controls, he used drug-free specimens of urine at hydrogen ion concentrations of 5.1, 5.0, 4.9 and 4.8. He found that there was a sharp dividing line in the growth of streptococci in the controls in urine at a  $p_H$  between 5.0 and 4.9. At a  $p_H$  of 5.1 and at a  $p_H$  of 5.0 there was marked growth in all experiments, whereas at a  $p_H$  of 4.8 there was absolutely no growth. Thus, by means of acidity alone Helmholz was able to obtain a bactericidal effect on *Str. faecalis*. He also found that at a  $p_H$  of 5.0 there was growth of practically all strains of *Str. faecalis*, but that the addition of only 10 mg. of sulfathiazole produced a 100 per cent bactericidal effect. At a  $p_H$  of 5.5 there was some inhibition of growth at all concentrations of the drug from 10 to 100 mg. per hundred cubic centimeters. At a  $p_H$  of 6.0 bactericidal activity was present only with concentrations of 50 and 100 mg. of the drug. At a  $p_H$  of 6.5 no bactericidal or bacteriostatic activity occurred with concentrations of 10, 20 and 30 mg. of the drug, and only slight bacteriostasis was noted with concentrations of 50 and 100 mg. Helmholz also studied the relative effects of 100 mg. of sulfathiazole and sulfanilamide on three

67. Helmholz, H. F.: The Use of Sulfathiazole as a Urinary Antiseptic, *J. Urol.* 45:135-145 (Jan.) 1941.

68. Helmholz, H. F., and Alford, H.: The Bactericidal Action of Sulfathiazole on the *Streptococcus Faecalis*. *Proc. Staff Meet., Mayo Clin.* 16:737-744 (Nov. 19) 1941.

strains of *Str. faecalis* at a  $p_H$  of 5.5, of 6.0 and of 6.5, and noted that when sulfanilamide was employed the streptococci grew out abundantly, whereas when sulfathiazole was used the number of colonies was reduced in all three strains at a  $p_H$  of 5.5 and in two strains at a  $p_H$  of 6.0 and of 6.5. Helmholtz deduces, on the basis of these experiments, that growth of *Str. faecalis* in urine is inhibited at a  $p_H$  of 4.9 and that sulfathiazole has a greater bactericidal action when the  $p_H$  is low. Furthermore, he is of the opinion that sulfathiazole is definitely superior to sulfanilamide in its bactericidal action on *Str. faecalis*.

Fisher and Haag<sup>69</sup> state that sulfacetimide<sup>70</sup> administered orally to mice and dogs appears to be about a fourth as acutely toxic as sulfanilamide similarly administered. Doses of 5 Gm. of sulfacetimide per kilogram of body weight administered orally to dogs were better tolerated, that is, produced fewer signs of acute poisoning than were observed among the same dogs after the administration of 2 Gm. of sulfanilamide per kilogram of body weight.

The rate of growth of young rats maintained on a diet containing 1.5 per cent of sulfacetimide showed no significant retardation as compared to that of control animals maintained on a similar diet not containing the drug. Two dogs which received 0.4 Gm. of sulfacetimide per kilogram of body weight daily for eleven weeks exhibited no loss of weight, no significant changes in the number of leukocytes or erythrocytes or in the value for hemoglobin, and no demonstrable pathologic changes in the liver, spleen, kidneys, adrenal bodies, stomach or intestines. The daily administration of 1 Gm. of sulfacetimide per kilogram of body weight was not tolerated for eleven weeks by 2 of 3 dogs for which such a regimen was initiated. Although necropsy of the 2 dogs did not reveal causative anatomic changes in the kidneys, results of studies of blood chemistry suggested that failure of the excretory function of the kidneys was probably responsible in large degree for the death of the 2 animals. The 1 animal living at the end of the eleven week period was not found to have any abnormalities of the tissues at necropsy. Among mice and dogs, a given concentration of sulfacetimide in the blood is less likely to be accompanied by signs of intoxication, regardless of the dose required to produce this concentration, than is a similar concentration of sulfanilamide in the blood. Fisher and Haag believe that there is evidence which suggests that sulfacetimide is more readily absorbed and eliminated by the mouse and by the dog than is sulfanilamide.

69. Fisher, R. S., and Haag, H. B.: Studies of the Comparative Toxicity, Absorption and Elimination of Sulfacetimide and Sulfanilamide, *J. Urol.* **47**:183-195 (Feb.) 1942.

70. Acetylsulfanilamide.

Schultz, Shidler and Niebauer <sup>71</sup> report a case in which acute urinary suppression followed the use of sulfadiazine. They report the signs and symptoms of beginning renal failure during the period of use of sulfadiazine as being microscopic and gross hematuria, crystalluria, pain in the abdominal region and the flanks, a decreased output of urine and nausea and vomiting. Their treatment consists of the forcing of fluids and of alkalization of the urine. If the output of urine decreases considerably, cystoscopic examination, ureteral catheterization and lavage are immediately indicated, with the institution of continuous urinary drainage by means of indwelling ureteral and vesical catheters. Subsequently, the renal pelvis should be irrigated with a 2 per cent solution of sodium bicarbonate every three to four hours. Catheters are to be removed when the output of urine has returned to normal. The deposition of sulfadiazine crystals in the renal pelves and ureters produces mechanical anuria. Sodium bicarbonate in amounts sufficient to alkalize the urine should be administered simultaneously with sulfadiazine.

Newman and Shleser <sup>72</sup> report a case of renal calculus due to sulfapyridine and sulfanilamide. The patient, a man 38 years old, had received these drugs for pneumonia. Two years later a roentgenogram revealed the shadow of a large renal calculus in the right renal area. The urine contained blood cells, and culture disclosed bacilli of the genus *Proteus*. At operation two stones were removed from the pelvis of the kidney; they were of the earthy, phosphatic type. Chemical analysis revealed large quantities of sulfonamide compounds mixed with the protein.

Winsor and Burch <sup>73</sup> discuss the renal complications which can follow sulfathiazole therapy and report 6 cases which illustrate some of the renal problems encountered in such therapy. Injury has been noted as resulting more from sulfapyridine therapy than from sulfathiazole therapy. This situation most probably is due to the fact that the latter drug has been used for only a relatively short time. It is too early to evaluate the status of sulfadiazine and sulfaguanidine, so far as renal damage is concerned. Sulfanilamide appears to be much less likely to injure the kidneys seriously. Winsor and Burch do not believe that the diagnosis of renal damage is difficult. The appearance of

71. Schultz, J. W.; Shidler, F. P., and Niebauer, J. J.: Acute Urinary Suppression Following Sulfadiazine Therapy, *J.A.M.A.* **119**:411-413 (May 30) 1942.

72. Newman, H. R., and Shleser, I. H.: Sulfonamide Renal Calculus Surgically Removed Two Years After the Administration of Sulfapyridine, *J. Urol.* **47**:258-261 (March) 1942.

73. Winsor, T., and Burch, G. E.: Renal Complications Following Sulfathiazole Therapy, *J.A.M.A.* **118**:1346-1353 (April 18) 1942.

hematuria, oliguria, backache, tenderness over one or both renal areas, decreased renal function, azotemia and progressive nephromegaly in a patient who has received sulfathiazole should make the physician suspect that renal damage has arisen from the drug. Cystoscopic study usually will establish the diagnosis. Sulfathiazole crystals in the urine may aid in establishment of the diagnosis, but their presence alone does not mean that renal damage has occurred. Roentgenologic study usually will not reveal uroliths unless there is calcification, which is rare. Winsor and Burch warn that because of the tendency of sulfathiazole to injure the kidneys it is necessary to employ the drug cautiously. First, the physician should determine whether or not the patient has had medication with a sulfonamide compound before. If the history is not reliable, it is advisable to determine the concentration of the drug in the blood and to prescribe accordingly. This will tend to prevent overdosage and to reduce the likelihood of injury to the kidneys. Second, the state of the patient's renal function and the nature of the urine being excreted should be evaluated before the physician begins to administer the drug. Third, the status of hydration of the patient should be evaluated. A severely dehydrated patient will take in much fluid and excrete but little and therefore will be more likely to experience renal damage. Fourth, an alkaline urine tends to reduce the formation of crystals, and if the use of alkalis and the maintenance of an alkaline urine are not contraindicated in a particular case, it would be well to administer alkalis and to maintain an alkaline urine. Fifth, there is some evidence to indicate the development of hypersensitivity to sulfonamide compounds. It is well, therefore, to be extremely cautious and particularly vigilant in the treatment of patients who already suffer from a form of allergy. Administration of the drug should be stopped immediately, once the slightest evidence of renal damage is discovered. Winsor and Burch recommend that fluids be administered in large quantities. Ureteral catheterization should be carried out promptly, and the catheter should be allowed to remain in place until a normal volume of urine flow has been reestablished. The renal pelves should be irrigated at two hour intervals with warm (107 F., or 41.6 C.) distilled water. Diuretic agents should have the form of large quantities of fluid and, if necessary, hypertonic solutions of dextrose. If possible the use of magnesium sulfate should be avoided, because it predisposes to the formation of sulfhemoglobin; but it may be used intravenously if cyanosis is not present and if the oliguria persists after other measures to induce diuresis have failed. Mercury and acid diuretic agents should not be used. The patient should be maintained on an alkaline ash diet, and the urine should be kept alkaline with the use of sodium bicarbonate. The intake of protein should be restricted for four or five days, or during the period of severe oliguria.

hematuria and azotemia. Fluids should be administered in large quantities for many days after the kidneys have returned to normal.

Lindner and Atcheson<sup>74</sup> state that the use of sulfathiazole may lead to very serious renal sequelae, and that the physician always should be alert to detect these sequelae when the drug is used. The patient's urine should be checked daily as to volume of output, hematuria, crystals, albuminuria and casts; and the intake of fluids should be known. Sulfathiazole is rapidly excreted in the urine and tends to precipitate, especially if the urine is acid. In use of the drug, care must be taken to see that sufficient fluids accompany it. Lindner and Atcheson point out that the concentration of sulfathiazole in the blood does not indicate the degree to which the crystals are precipitated. Sulfathiazole concretions are not radiopaque. The crystals tend to produce multiple hemorrhages throughout the renal parenchyma and mucosal linings. Such hemorrhages may even be of advanced degree, with massive destruction of parenchyma. The crystals may produce anuria by mechanical block in the ureters, but it is more likely that the serious blockages are those which occur in the tubules. Lavage and removal of blockage at the lower level will lead to an increased output of urine, up to a certain point. Lindner and Atcheson report that the best therapy at present is renal lavage carried out with warm water by means of ureteral catheters supplemented by the forcing of fluids, alkalization of the urine and the use of heat.

Hughes, Sayen and LaTowsky<sup>75</sup> state that a collection of crystals of sulfadiazine forming actual urinary calculi may occur in the urinary tract. Obstruction to the flow of urine may or may not occur because of these collections. If obstruction does occur, it can be treated successfully by bilateral ureteral catheterization and the forcing of fluids. In the reported case, the urine was persistently acid. It has been shown that sulfadiazine is less soluble in acid urine than in alkaline urine. Maintenance of an alkaline urine might have aided in prevention of the complication of crystal agglomeration.

#### URINARY INFECTION

Heldfond<sup>76</sup> presents an analysis of 145 cases of pyelonephritis of pregnancy and compared the results obtained with various chemotherapeutic agents. The distinct superiority of sulfonamide compounds was demonstrated, and of those used sulfapyridine was found to be the least effective and sulfathiazole by far the most effective.

74. Lindner, H. J., and Atcheson, D. W.: Sulfathiazole Crystallization in the Kidney, *J. Urol.* **47**:262-266 (March) 1942.

75. Hughes, P. B.; Sayen, J. J., and LaTowsky, L. W.: Sulfadiazine Calculi in the Urinary Tract: Report of a Case, *J. Urol.* **47**:274-276 (March) 1942.

76. Heldfond, A.: The Treatment of Urinary Tract Infections of Pregnancy, *West. J. Surg.* **50**:82-84 (Feb.) 1942.



## DILATATION OF URINARY TRACT

Treite<sup>77</sup> states that all the cavities of the urinary tract may undergo congenital enlargement, such as hydronephrosis, megaloureter and megacystitis. There is no sharp demarcation, he said, between extreme dilatation and normal size. Occasionally, there are associated anomalies of other organs, such as dilatation of the intestinal tract (megaesophagus and megacolon, also called "Hirschsprung's disease"). Enlargements of the female genital tract also have been noted, such as hydrometra and hydrocolpos. Treite reported 13 cases of fetal enlargement of the bladder. The patients were observed in Stoeckel's clinic in Berlin. From the genetic standpoint, the condition is divided into three types. First is megacystitis, an anomaly of genesis or so-called excess formation, often associated with other excess formations of the urinary tract, such as hydronephrosis and hydroureter. The wall of the bladder shows an abnormal thickness, including both the muscular and the mucous layer, in spite of the size of the organ. Second is enlargement of the bladder by distention (constriction of the neck of the bladder and obstruction of the urethra). The walls are thin and smooth, without folds. Patients have been observed who exhibited formation of valves of the urethral orifice and also complete atresia of the urethral outlet. Secretion of urine normally does not exist during fetal life; hence, true distention of the bladder can occur only postnatally or by marked disturbance of placental metabolism and circulation. Third, there are many cases in which the walls of the bladder are definitely distended but in which no urethral obstruction is found. In these cases other megaf ormations of the urinary tract are rarely found, but not uncommonly there is an associated megacolon. Distention of the bladder without anatomic reason usually is caused by functional factors of nervous origin, such as (1) hyperfunction of the sympathetic nerves, (2) persistence of the aorticolumbar paraganglion (Zuckerkindl's organ) and (3) intervention of the hypogastric nerve. Treite also considers that among pregnant women hormonal factors may cause distention of most of the organs of the female pelvis.

## UROGRAPHY

Goldburgh and Baer<sup>78</sup> report a case in which death followed the intravenous administration of 3,5-diiodo-4-pyridone-N-acetic acid diethanolamine (diodrast). The patient was elderly and had complained of numerous conditions. She had had diabetes for fifteen years and had

77. Treite, P.: Zur Pathologie der angeborenen Harnblasenerweiterungen. *Ztschr. f. Urol.* **35**:117-140, 1941.

78. Goldburgh, H. L., and Baer, S.: Death Following the Intravenous Administration of Diodrast, *J.A.M.A.* **118**:1051-1052 (March 28) 1942.

been attending the cardiac disease, metabolism, arthritis and allergy departments of a hospital for years. A urogram was made with the intravenous technic because of a palpable, tender right kidney. The patient had no difficulty, and nine days later a second urogram was made with the same intravenous technic. A few drops of a mixture of the aforementioned contrast medium was placed under the patient's tongue; this procedure caused no reaction. Then 25 cc. of a 35 per cent solution of the contrast medium was injected within a period of seven minutes. Five minutes later unconsciousness developed, and the patient died twenty minutes after the beginning of the injection. Goldburgh and Baer consider that her death was due to the anaphylactic reaction which followed the intravenous injection of the contrast medium. Cases occasionally are reported, of the occurrence of death after excretory urography. Study of most of these cases suggests that an anaphylactic reaction resulted. Goldburgh and Baer suggest that a detailed history with special inquiry as to allergy should be taken and that the patient's sensitivity should be tested before excretory urography is attempted.

Tzschirntsch<sup>79</sup> discusses injuries which can follow retrograde pyelography. He states that damage to the renal parenchyma may result from distention of the renal pelvis and also that the mucosa of the renal pelvis may be injured by the medium, either by corrosion of the mucous membrane or by resorption of the metallic elements in the solution. Injury caused by the ureteral catheter is much more frequent than injury caused by the injected solution. Tzschirntsch reports 2 cases in which injury to the calices had been inflicted by ureteral catheters. The damage was proved at operation. In both cases the mucosa of the calices was perforated by the catheter. This was followed by deposition of contrast medium in the renal parenchyma. In 1 of these cases there was evidence of sclerosis and destruction of the involved renal tissue. In the second case there was complete absorption of the injected material, but secondary renal stones developed some years later. In both cases there were typical clinical manifestations of reaction to the injection. A sharp pain occurred immediately after the injection of 2 or 3 cc. of the contrast medium and was followed by serious renal pain and infection which persisted for several weeks. According to Tzschirntsch perforations by catheters can be avoided if physicians will be careful never to use a ureteral stylet. Also, the ureteral catheter never should be passed beyond the lower part of the renal pelvis. This region can be determined by noting the markings on the catheter and by the regularity with which urine drips from the tip of the ureteral catheter.

79. Tzschirntsch, K.: Die instrumentelle Schädigung der Nieren durch die retrograde Pyelographie, *Ztschr. f. Urol.* 35:69-77. 1941.

## ANESTHESIA

Townsend<sup>80</sup> maintains that anesthesia produced with pentothal sodium has been shown to be safe as or safer than anesthesia produced with other agents when it is employed for almost all types of urologic surgery. The only contraindication would seem to be extreme youth. The careful administration of pentothal sodium is absolutely essential to satisfactory results. The advantages of anesthesia produced by pentothal sodium have been shown by use of the method in cases of respiratory diseases. He states that the dangers of explosion in the operating room are entirely eliminated when this type of anesthesia is used. It is also the most pleasant type of anesthesia from the patient's point of view.

## TRANSMISSION OF GENITAL TUBERCULOSIS

Schmid<sup>81</sup> reports a case of transmission of tuberculosis. Six weeks after intercourse, the patient had a tuberculous ulcer of the vulva, and on examination it was found that her partner had tuberculous prostatitis and vesiculitis seminalis.

## HEMATURIA

Weyeneth,<sup>82</sup> in discussing the differential diagnosis of hematuria, reports 2 cases in which difficulties in diagnosis were encountered. In 1 case a papilloma was situated in the upper part of the ureter; in the other a pseudocyst filled with blood was found in the capsule of a kidney. This pseudocyst apparently had developed after trauma. Treatment consisted of nephrectomy in both cases.

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80. Townsend, J. M.: The Use of Pentothal Sodium in Urological Surgery, *J. Urol.* **47**:235-239 (March) 1942.

81. Schmid, M.: Primäre Inokulationstuberkulose der Vulva durch Kohabitation, *Schweiz. med. Wchnschr.* **70**:852-853 (Sept. 7) 1940.

82. Weyeneth, R.: Diagnostic différentiel des hématuries à propos de deux cas rares, *Schweiz. med. Wchnschr.* **71**:481-483 (April 5); 501-505 (April 12) 1941.

## EFFECTS OF LOWERING TEMPERATURE OF AN INJURED EXTREMITY TO WHICH A TOURNIQUET HAS BEEN APPLIED

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BALTIMORE

In 10 experiments<sup>1</sup> performed recently in which a tourniquet was applied to a severely injured extremity for a five hour period and in which treatment consisted in the administration of blood plasma, it was found that death occurred in all instances and that the average period of survival was only fourteen hours. In 10 other experiments which were identical in execution, except that a tourniquet was not used, 8 animals recovered and the remaining 2 lived four and twelve days, respectively.

The present experiments were performed in order to determine the systemic effects of reducing the temperature of an injured extremity to which a tourniquet has been applied.

### METHODS AND RESULTS

*Procedure.*—Large animals were used in all the experiments. Pain was prevented by the use of soluble pentobarbital U. S. P. (pentobarbital sodium) and morphine. Injury was caused by striking one of the posterior extremities many blows with a blunt instrument for five to eight minutes. A tourniquet was placed around the upper part of the injured thigh, and the extremity was surrounded by ice as soon as the traumatization was completed. The tourniquet was left in place for five hours. A total of 20 experiments was performed. In 10 of these, the intravenous administration of plasma was begun immediately after the tourniquet was removed. The total quantity of plasma injected corresponded to 5 per cent of the body weight of the recipient. With 2 exceptions, plasma was injected slowly over a five hour period. In the remaining 10 experiments no plasma was injected. In all the experiments the injured extremity was surrounded by ice for an eleven hour period.

*Trauma; Tourniquet; Cold; Plasma.*—Except for the cooling of the injured part, these experiments were performed in the same manner as those reported previously, in all of which the animals died. In the present experiments 5 of the 10 animals recovered.

From the Department of Surgery of the Johns Hopkins University and Hospital.

1. Duncan, G. W., and Blalock, A.: The Effects of the Application of a Tourniquet on the General Response to Gross Trauma to an Extremity, Surgery, to be published.

TABLE 1.—The Effects of Trauma to the Leg, Application of a Tourniquet, Cooling of the Injured Part and Intravenous Injection of Blood Plasma

Experiment Number	Dog, Weight, Kg.	Duration Tourniquet, Hours	Plasma Infected, Percentage of Body Weight	Hematocrit Reading				Temperature, Rectal, F.				Survival Time, Hours	Result	Regional Loss of Fluid, Percentage of Body Weight
				Control		5 Hours		Control		5 Hours				
				Control	5 Hours	Control	5 Hours	Control	5 Hours	Control	5 Hours			
1	7.5	5	11	5	47.0	40.0	25.0	102.8	97.4	84.2	84.2	22	Death	8.7
2	0.1	5	11	5	34.0	37.3	29.7	101.6	96.8	80.4	80.4	..	Recovery	..
3	6.2	5	11	5	41.7	44.5	35.5	101.7	95.4	88.2	88.2	..	Recovery	..
4	6.7	5	11	5	43.7	37.5	34.2	101.4	98.8	90.0	90.0	..	Recovery	..
5	9.2	5	11	5	48.3	44.4	38.0	102.3	96.1	84.0	84.0	17	Death	5.1
6	6.7	5	11	5	36.4	30.3	31.7	100.0	93.2	90.4	90.4	..	Recovery	..
7	5.7	5	11	5	47.0	44.8	30.7	101.4	93.8	87.4	87.4	..	Recovery	..
8	7.1	5	11	5	48.2	45.0	49.0	98.0	87.4	72.4	72.4	17	Death	3.5
9	10.1	5	11	5	37.2	43.8	34.8	103.2	96.0	77.5	77.5	17	Death	4.8
10	8.4	5	11	5	35.5	39.0	41.0	101.4	95.8	80.2	80.2	15	Death	5.1

TABLE 2.—The Effects of Trauma to the Leg, Application of a Tourniquet and Cooling of the Injured Part (No Plasma Administered)

Experi- ment Number	Dog, Weight, Kg.	Dura- tion Tourni- quet, Hours	Dura- tion Ice Pack, Hours	Hematocrit Reading				Temperature, Rectal, F.				Survival Time, Hours	Result	Regional Loss of Fluid, Percentage of Body Weight				
				Control		5 Hours		10 Hours		Control					5 Hours		10 Hours	
				Control	5 Hours	Control	5 Hours	Control	10 Hours	Control	5 Hours				Control	5 Hours	Control	10 Hours
11	8.7	5	11	51.3	52.0	61.4	101.0	98.0	83.8	20	Death	3.9						
12	8.8	5	11	31.8	34.4	33.7	103.0	99.3	80.4	..	Recovery	...						
13	7.0	5	11	41.0	40.8	50.2	102.3	96.5	80.4	..	Recovery	...						
14	6.7	5	11	39.0	52.0	51.3	102.2	95.0	....	38	Death	7.1						
15	9.2	5	11	41.0	40.0	51.4	102.0	97.4	95.1	19	Death	5.2						
16	10.3	5	11	44.0	40.4	50.0	101.8	93.2	83.0	17	Death	4.4						
17	5.8	5	11	40.0	40.0	40.3	102.7	94.0	74.2	21	Death	0.5						
18	9.1	5	11	40.8	36.4	51.2	98.4	90.2	78.4	..	Recovery	...						
19	8.5	5	11	34.3	37.2	42.3	101.0	91.4	88.0	..	Recovery	...						
20	8.0	5	11	43.0	52.4	57.7	102.5	97.8	88.2	19	Death	5.5						

The alterations in the hematocrit readings were variable; a dilution occurred in the majority of the studies. A marked decline in the rectal temperature took place in all the experiments. This was undoubtedly due in part to the proximity to the rectum of the ice which was encasing the injured extremity. The decline in rectal temperature usually occurred more rapidly after the removal of the tourniquet. As stated previously, 5 of the 10 animals recovered. The survival period of the remaining 5 ranged from fifteen to twenty-two hours. The average loss of fluid into the injured part in these experiments equaled 5.4 per cent of the body weight. The results of these experiments are given in table 1.

*Trauma; Tourniquet; Cold.*—The other 10 experiments differed from those in the preceding group only in that the injection of blood plasma was not included. Four of the 10 animals recovered.

TABLE 3.—*Showing the Ill Effects of a Tourniquet and the Beneficial Effects of Lowering the Temperature of a Part Distal to a Tourniquet*

Experimental Procedures	Number of Experiments	Tourniquet Applied, Hours	Plasma Therapy, Percentage of Body Weight	Number of Animals Surviving	Average Survival Period of Remainsder	Regional Fluid Loss, Percentage of Body Weight
Trauma; plasma therapy (no tourniquet)	10	0	5	8	8 days	....
Trauma; tourniquet; plasma therapy	10	5	5 to 10	0	14 hr.	7.8
Trauma; tourniquet; cold; plasma therapy	10	5	5	5	17 hr. 36 min.	5.42
Trauma; tourniquet; cold (no plasma)	10	5	0	4	23 hr. 20 min.	5.41

There was an increase in the hematocrit reading in most of the experiments and also a great decline in the rectal temperature. As stated, 4 of the 10 animals survived. The survival periods of the remaining 6 ranged from seventeen to thirty-eight hours, the average being approximately twenty-three hours. The average difference in the weights of the injured and of the noninjured parts in these experiments equaled 5.41 per cent of the body weight. The results of these studies are given in table 2.

#### COMMENT

In the previous experiments reported by Duncan and me it was noted that the application of a tourniquet to a severely traumatized extremity for a period of five hours greatly decreased the chances of survival of the animal. The present experiments show that cooling of the part distal to the tourniquet lessens the ill effects of shutting off and then releasing the blood supply to an injured part. The results

which were observed when the extremity distal to a tourniquet was cooled were almost as good as those noted when the application of ice was supplemented by the injection of plasma. The results of all these experiments are summarized in table 3.

These observations, as well as those reported previously on crush injuries,<sup>2</sup> indicate that the addition of local ischemia and anemia to trauma results in more deleterious effects than are caused by trauma alone. The general effects of trauma on the one hand and of trauma plus ischemia and anemia on the other may be very different. Furthermore, the present results, the previous experiments on crush injuries and the observations of Allen<sup>3</sup> and of Brooks and Duncan<sup>4</sup> indicate that the harmful effects of a tourniquet will be lessened if the temperature of the part distal to the constriction is lowered by suitable means. This may be due to a slowing of metabolic processes or to a number of other alterations.

The results of the experiments reported here indicate that the use of a tourniquet on an injured extremity should be avoided whenever possible, but that if some form of constriction is necessary the temperature of the distal ischemic and anemic part should if possible be lowered by artificial means.

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2. Duncan, G. W., and Blalock, A.: The Uniform Production of Experimental Shock by Crush Injury: Possible Relationship to Clinical Crush Syndrome, *Ann. Surg.* **115**:684, 1942; Shock Produced by Crush Injury: Effect of Administration of Plasma and Local Application of Cold, *Arch. Surg.* **45**:183 (Aug.) 1942.

3. Allen, F. M.: Surgical Considerations of Temperature in Ligated Limbs, *Am. J. Surg.* **45**:459, 1939.

4. Brooks, B., and Duncan, G. W.: Effects of Temperature on Survival of Anemic Tissue: Experimental Study, *Ann. Surg.* **12**:130, 1940.

# DELETERIOUS EFFECTS OF ANOXIA ON THE LIVER OF THE HYPERTHYROID ANIMAL

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AND

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It has been recognized for some time that persons with thyrotoxicosis and animals in which a state of hyperthyroidism has been artificially produced are particularly sensitive to anoxia. The extraordinary sensitivity of thyroid-fed rats to want of oxygen was first brought out by Asher and Duran,<sup>1</sup> who showed that animals with hyperthyroidism did not tolerate even minor degrees of anoxia. The behavior picture presented by the rats in their experiments was characterized by dyspnea, unrest and convulsive movements; the animals finally became unable to move, were obviously dangerously ill and died unless air was given. Normal rats at the same oxygen tension were relatively unaffected. Streuli and Asher<sup>2</sup> had earlier found the converse to be true, namely, that thyroidectomized rats were able to tolerate a lack of oxygen which brought normal animals to the point of death by asphyxiation. In 1941 Barach and associates<sup>3</sup> confirmed the work of Streuli and Asher, demonstrating that after thyroidectomy rats show a remarkable increase in resistance to low oxygen tensions, such as those encountered in high altitudes. In their experiments the majority of thyroidectomized rats survived for three weeks in a chamber in which the oxygen was kept at 6 per cent (corresponding to an altitude of 31,500 feet [9.6 kilometers]), whereas normal rats kept in a similar atmosphere died in twelve to thirty-six hours.

In a survey of the literature no studies were found dealing particularly with the effects of anoxia on the liver during hyperthyroidism. That the

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From the Surgical Research Laboratory, Mary Imogene Bassett Hospital.

1. Asher, L., and Duran, M.: *Beiträge zur Physiologie der Drüsen*: XLIV. Das Verhalten von normalen, mit Schilddrüsensubstanz gefütterten und schilddrüsenlosen Ratten gegen reinen Sauerstoffmangel, *Biochem. Ztschr.* **106**:254, 1920.

2. Streuli, H., and Asher, L.: *Beiträge zur Physiologie der Drüsen*: XXXVI. Das Verhalten von schilddrüsenlosen, milzlosen, schilddrüsen- und milzlosen Tieren bei O<sub>2</sub>-Mangel, zugleich ein Beitrag zur Theorie der Bergkrankheit, *Biochem. Ztschr.* **87**:359, 1918.

3. Barach, A. L.; Eckman, M., and Molomut, N.: Modification of Resistance to Anoxia, with Especial Reference to High Altitude Flying, *Am. J. M. Sc.* **202**: 336, 1941.



liver in particular might suffer from want of oxygen seems reasonable. The cells of the liver are always nearer the point of asphyxiation than other cells of the body owing to the fact that only 25 per cent of their blood supply is arterial.<sup>4</sup> It may be assumed that the increased demands on the liver for oxygen during hyperthyroidism<sup>5</sup> leave a narrow margin of safety. Also, as shown in previous studies, the liver under conditions of hyperthyroidism is particularly susceptible to injury.<sup>6</sup>

The present paper records our experiments on the effect of anoxia on the liver during artificial hyperthyroidism.

#### METHOD AND MATERIALS

The experiments were carried out on male albino rats having an initial weight of between 150 and 175 Gm. The standard diet consisted of Purina dog chow, and in addition each rat was given 0.4 Gm. of yeast three times a week. Hyperthyroidism was produced by the subcutaneous injection of crystalline thyroxin<sup>7</sup> daily over a period of approximately two to three weeks in doses of 0.1 mg.

Autopsy was performed as soon as possible on animals that died, and blocks of tissue from the liver and other organs were fixed in Zenker's solution and in 1.6 per cent solution of formaldehyde. Animals that were killed were given a sharp blow at the base of the skull; autopsy was carried out immediately. When determinations of glycogen were to be carried out, the liver was removed within thirty seconds; a portion of the liver was immediately fixed in absolute alcohol for subsequent staining with Best's carmine, and the glycogen was determined according to the method of Good, Kramer and Somogyi.<sup>8</sup>

The apparatus used in the experiments on anoxia consisted of a bell jar 8 inches (20 cm.) in diameter and 12 inches (30.5 cm.) high set on a greased plate of ground glass and containing a wire gauze platform on which the rat was placed suspended over a pan of soda lime and calcium chloride. A two hole stopper at the top of the bell jar contained a thermometer and an exit tube. The bell jar was connected with a 40 liter spirometer which served as a reservoir for the gas mixtures used in the experiments. The mixtures were made by diluting room air in the spirometer with nitrogen until the desired percentage of oxygen was obtained. The gas mixture from the spirometer was run continuously through the bell jar. Samples of the mixture were drawn at frequent intervals from the

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4. Best, C. H., and Taylor, N. B.: *The Physiological Basis of Medical Practice*, ed. 2, Baltimore, Williams & Wilkins Company, 1940, p. 468.

5. Reinwein, H., and Singer, W.: Studien über die Gewebsatmung: IV. Der Einfluss von Thyroxin, Adrenalin und Insulin auf den Sauerstoffverbrauch überlebender Leberzellen, *Biochem. Ztschr.* **197**:152, 1928.

6. (a) McIver, M. A.: Increased Susceptibility to Chloroform Poisoning Produced in the Albino Rat by Injection of Crystalline Thyroxin, *Proc. Soc. Exper. Biol. & Med.* **45**:201, 1940. (b) McIver, M. A., and Winter, E. A.: Further Studies on Increased Susceptibility to Chloroform Poisoning Produced in the Albino Rat by Injection of Crystalline Thyroxin, *J. Clin. Investigation* **21**:191, 1942.

7. The crystalline thyroxin for this work was supplied by E. R. Squibb & Sons, New York.

8. Good, C. A.; Kramer, H., and Somogyi, M.: The Determination of Glycogen, *J. Biol. Chem.* **100**:485, 1933.

exit tube and analyzed on a portable Haldane apparatus in order to check the concentration of oxygen.

The rats were placed singly in the bell jar and subjected for varying periods to the low concentrations of oxygen. In the early experiments the periods of exposure were short, both for controls and for thyroxin-treated rats, and occurred on successive days. In the later experiments slightly higher percentages of oxygen were in general used; the periods of exposure were considerably longer and were completed in one day.

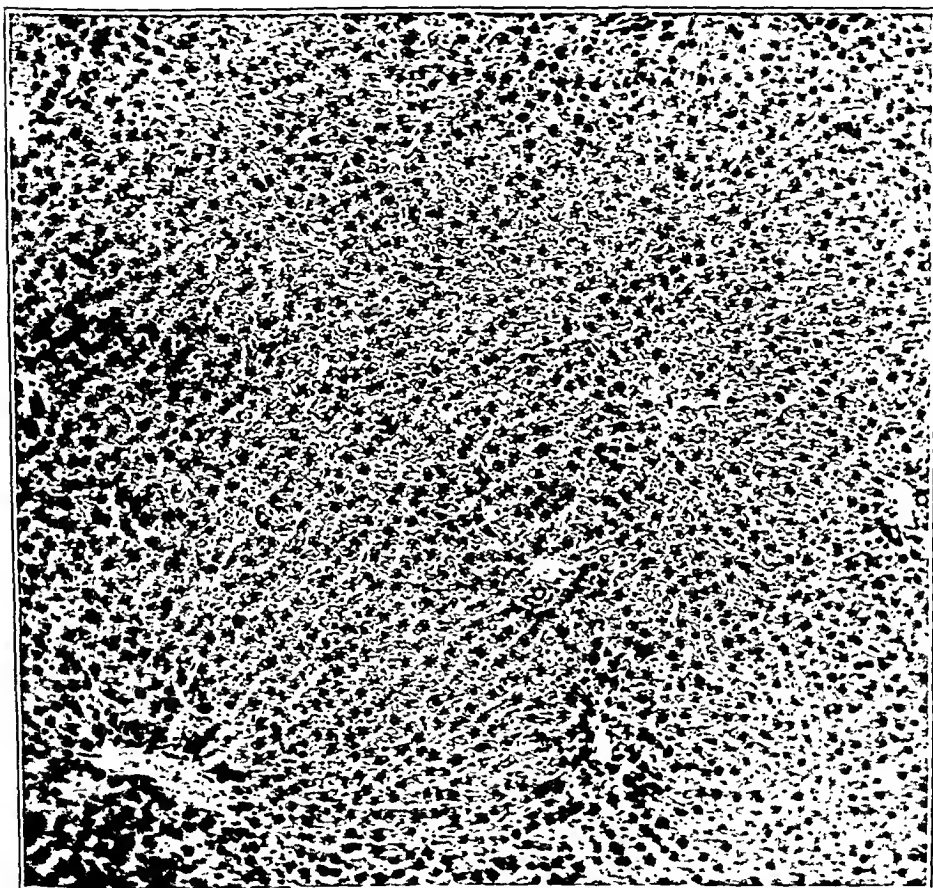


Fig. 1.—Section of the liver stained with hematoxylin and eosin, taken from control rat 6 after anoxia of nine and a half hours' duration. The concentration of oxygen was 11.2 per cent. There is no evidence of damage to the liver. (Magnification,  $\times 100$ .)

#### PRELIMINARY OBSERVATIONS ON ANIMALS RECEIVING CRYSTALLINE THYRONIN

The various statements concerning thyroxin-treated rats are based on data acquired during the past two years on 186 rats.

The animals were usually kept for at least one week before the injections of thyroxin were started. This was done to make sure that they were all in healthy condition and to allow them to become adjusted to the laboratory environment. They were weighed three times a week, and their body temperatures were taken by rectum at the same time or in certain instances more frequently.

While the animals were receiving daily injections of thyroxin, they remained in general in good condition, as judged by appearance, state of the hair and activity.

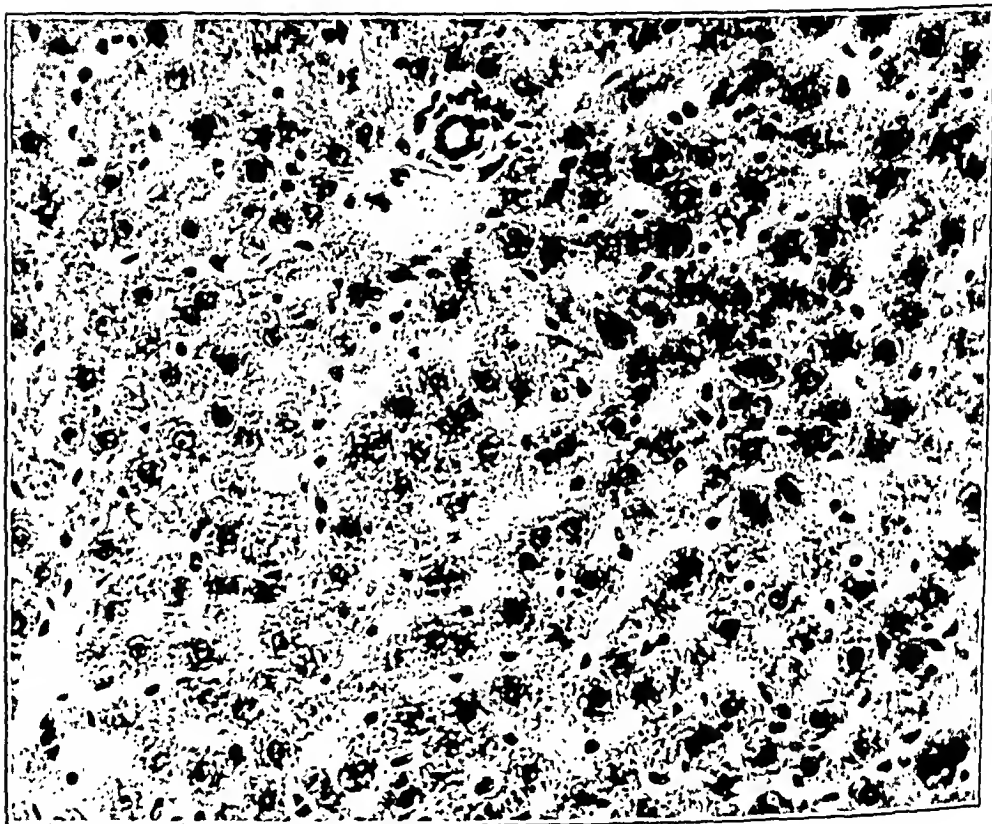


Fig. 2.—Higher magnification ( $\times 300$ ) of the section shown in figure 1.

*Weight.*—Control rats gained progressively throughout the period of observation, showing an average gain in weight of 2.6 Gm. per day. Approximately 70 per cent of the rats receiving crystalline thyroxin showed an initial drop in weight lasting from two to five days and amounting roughly to about 10 Gm. After this drop the weight was usually maintained until about the tenth day, from which time there was a slow gain. About 18 per cent gained weight slowly but continuously throughout the period of injections. The remaining 12 per cent had an erratic weight course, which is not readily classified.

*Food Intake.*—In the early stages of administration of thyroxin most of the rats showed a loss of appetite; during this stage they were frequently restless and mild diarrhea often developed. After the first week or ten days, however, the appetite returned and the amount of food consumed was greater than that taken by the controls.

*Body Temperature.*—The hyperthyroid rats frequently had a somewhat higher rectal temperature than the controls. Although there was

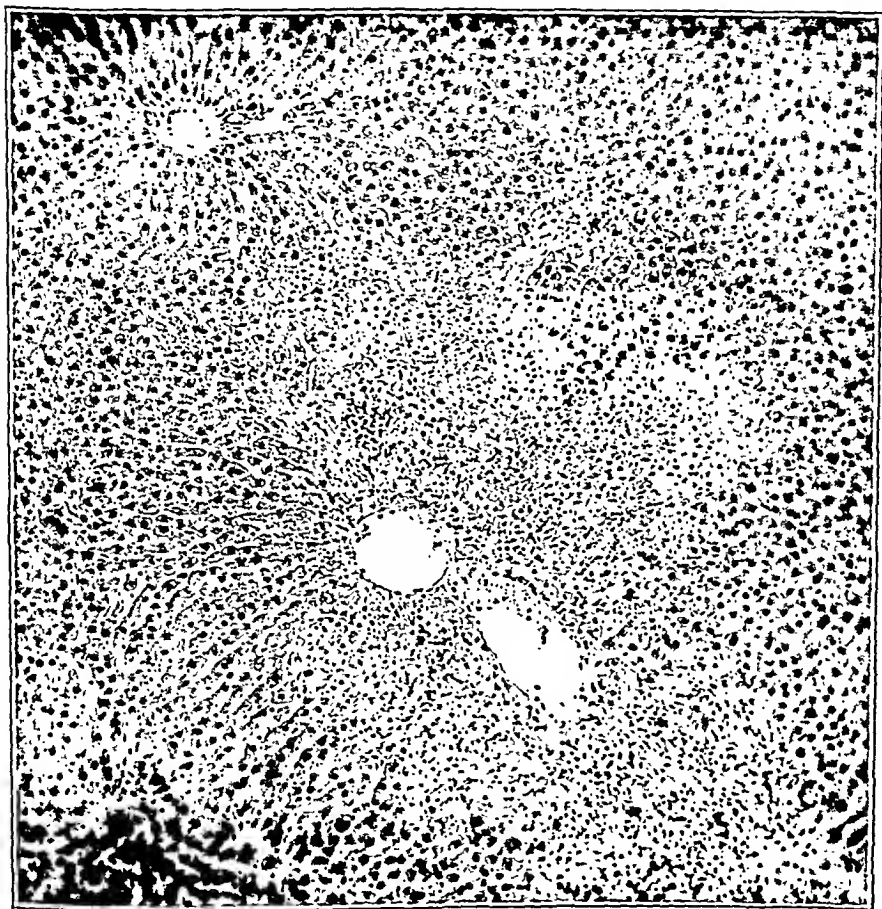


Fig. 3.—Section of the liver stained with hematoxylin and eosin, taken from rat 4, which went through a preliminary period of administration of thyroxin followed by anoxia of nine and a half hours' duration. The concentration of oxygen was 11.2 per cent. Areas of degeneration are shown. (Magnification,  $\times 100$ .)

an average difference of only 0.3 C. (0.5 F.) in temperature between the two groups (that of the normal rats averaging 36.5 C. [97.7 F.] and that of the hyperthyroid rats 36.8 C. [98.2 F.]), none of the normal rats had a temperature as high as 37 C. (98.6 F.), whereas a number of the hyperthyroid rats had temperatures of 37 C. or slightly higher.

*Hepatic Glycogen.*—With the standard diet which we employed, the hepatic glycogen in control animals, as previously reported,<sup>9b</sup> varied from 7.1 to 5.0 Gm. per hundred cubic centimeters. In 39 thyroxin-treated rats on the same diet the glycogen level varied from 3.2 to 0.18 Gm. per hundred cubic centimeters, only 2 animals having a level above 1.6 Gm.

*Histologic Examination of the Liver.*—A study of the pathologic material from 31 rats that had been killed<sup>9</sup> after receiving injections of

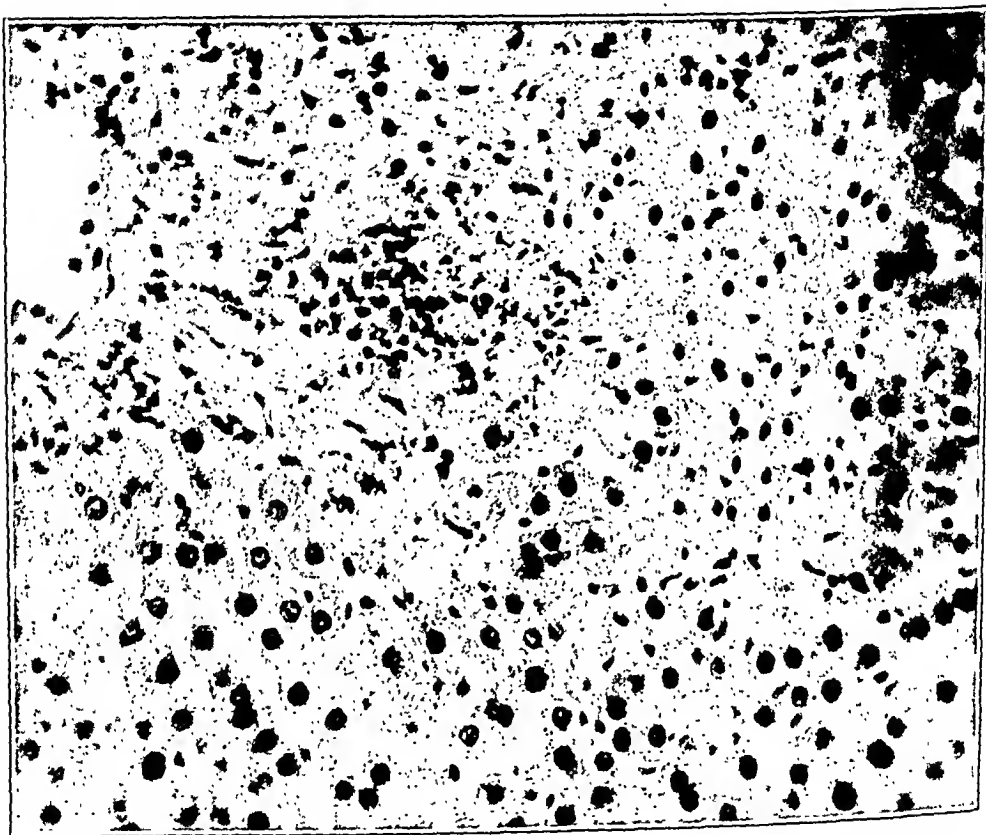


Fig. 4.—Higher magnification ( $\times 300$ ) of the section shown in figure 3. Note the boundary zone between the necrotic area and relatively normal hepatic tissue.

9. There are a number of studies in which histologic changes are said to have been produced in the liver by the administration of thyroxin. The studies in which these changes were noted, however, were carried out with the use of large or even fatal doses of thyroxin (Farrant, R.: *Hyperthyroidism: Its Experimental Production in Animals*, Brit. M. J. 2:1363, 1913. Hashimoto, H.: *The Heart in Experimental Hyperthyroidism with Special Reference to Its Histology*, Endocrinology 5:579, 1921. Gerlei, F.: *Nécrose du foie consécutive à l'empoisonnement par la thyroxine*, Ann. d'anat. path. 10:555, 1933); in many cases these were given over long periods. An attempt was made in our experiments to use doses of

(Footnote continued on next page)

crystalline thyroxin over a period of approximately two to three weeks without exception failed to reveal any notable histologic abnormalities of the liver. Minor histologic differences were often found, however, when the cells were compared with those of the livers of normal well fed rats, the cells in the livers of thyroxin-treated rats being more homogeneous and compact. The appearance of these cells, however, did not

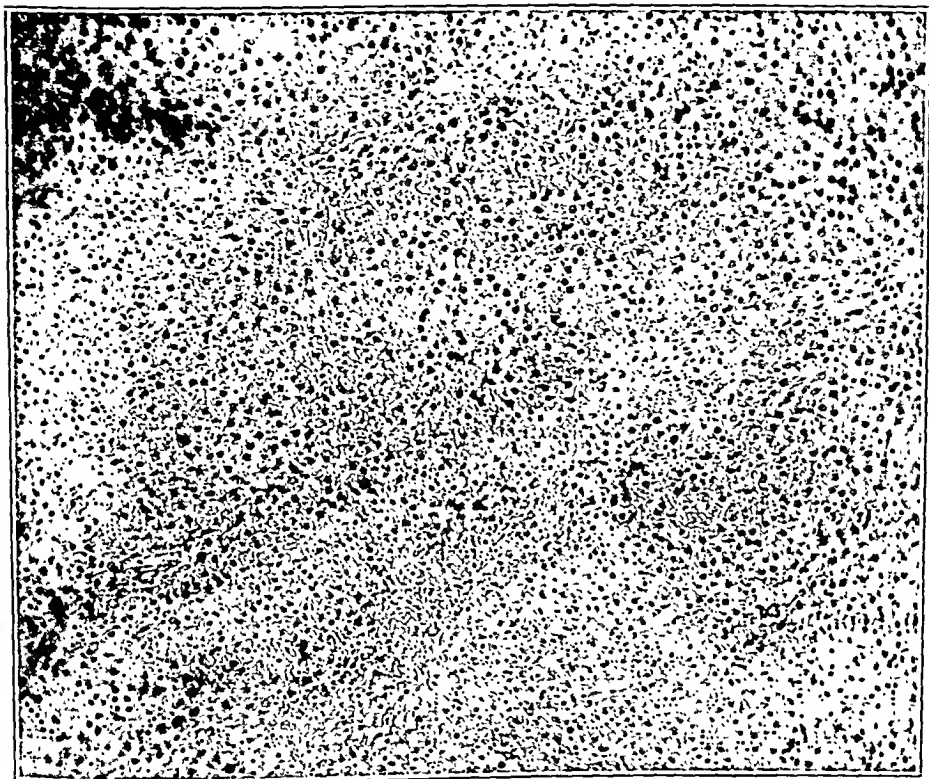


Fig. 5.—Section of the liver stained with hematoxylin and eosin, taken from rat 7, which went through a preliminary period of administration of thyroxin followed by anoxia of seven hours' duration. The concentration of oxygen was 11 per cent. Widespread necrosis of the liver is shown. (Magnification,  $\times 100$ .)

thyroxin which while producing definite hyperthyroidism would not be lethal. With such doses and over the period in which we employed the drug, it seems clear that it produces no important histologic changes in the liver. During a period of two years there were 186 rats that received crystalline thyroxin, and among these 12 deaths occurred, usually ascribed to the effects of intercurrent infection, frequently of the respiratory tract. Histologic examination of the liver was carried out on 10 of these animals, and in 4 instances degenerative changes were found. It is interesting in this connection that G. Haban (*Leberveränderungen bei experimentellem Hyperthyreoidismus*, *Beitr. z. path. Anat. u. z. allg. Path.* 95:573, 1935) in studying the effects of injections of crystalline thyroxin on the liver found important changes only when some intercurrent infection occurred.

differ particularly from that of hepatic cells of a starved animal and was probably due in both instances to the fact that the hepatic glycogen content was low.

#### OBSERVATIONS IN EXPERIMENTS ON ANOXIA

The behavior reaction of the hyperthyroid and of the normal animals when exposed to atmospheres containing approximately 11 per cent

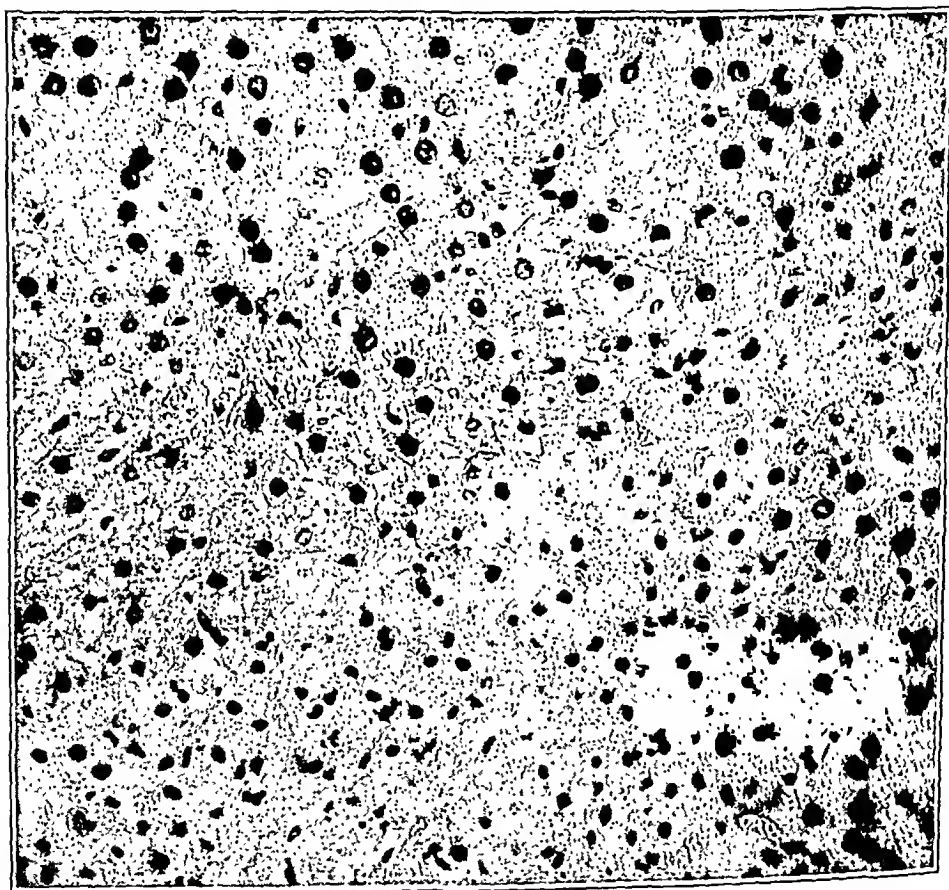


Fig. 6.—Higher magnification ( $\times 300$ ) of the section shown in figure 5.

oxygen in general showed marked differences. The normal animals for the most part slept quietly, and, although there was frequently some increase in their respiratory rate, they showed no signs of acute distress. The hyperthyroid animals, on the other hand, were restless and apathetic by turns. Their respiration became rapid and at irregular intervals was interrupted by a pause followed by a deep inspiration. They frequently assumed a position in which their heads were near the inlet of the bell jar. In general the behavior picture was similar to that described by Asher and Duran.<sup>1</sup>



The results of the experiments on anoxia are shown in tables 1 and 2. It will be noted that 26 rats were used; 17 of these had received injections of crystalline thyroxin over a period of approximately two to three weeks prior to being subjected to the low oxygen mixtures, while the 9 controls had received no thyroxin.

*Mortality.*—Nine of the 17 hyperthyroid rats died after varying periods of anoxia, which was in striking contrast to the absence of deaths

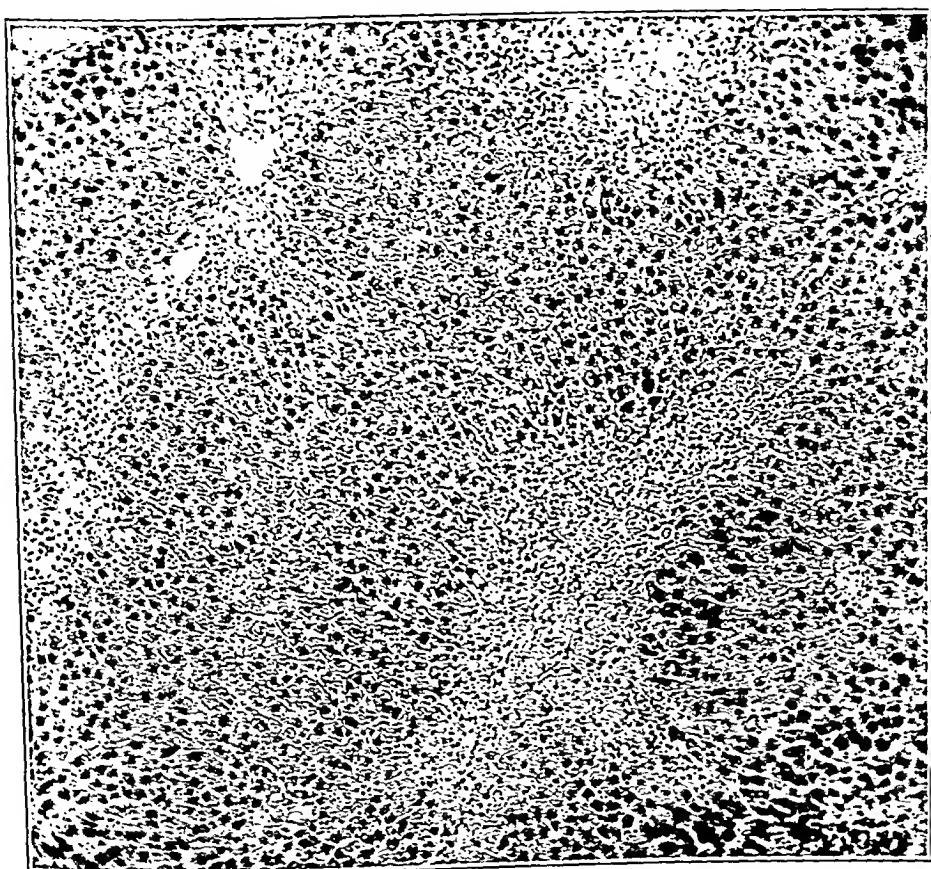


Fig. 7.—Section of the liver stained with hematoxylin and eosin, taken from rat 16, which went through a preliminary period of administration of thyroxin followed by anoxia of six and three-quarters hours' duration. The concentration of oxygen was 10.5 per cent. The animal was killed twenty-four hours after anoxia. Areas of degeneration are evident. (Magnification,  $\times 100$ .)

among the 9 control rats similarly exposed to low oxygen atmospheres. The first two hours in the low oxygen atmosphere seemed to be the most critical for the hyperthyroid rats, and, although an attempt was made to return them to room air as soon as it was evident that their condition was becoming precarious, 5 of them died after this short exposure, 2



TABLE 1.—*Experiments on Anoxia with Hyperthyroid Animals\**

Rat	Administration of Crystalline Thyroxin		Anoxia		Comment	Hepatic Glycogen, Gm. per 100 Cc.	Histologic Examination of Liver
	Total Amount, Mg.	Duration, Days	Oxygen, per Cent	Duration			
1	1.8	18	9.3 9.5 10.0 10.3 6.5	56 min. 58 min. 80 min. 61 min. 65 min.	Killed 2 hr. 15 min. after removal from bell jar	0.8	No noteworthy deviation from normal
2	1.6	16	9.3 9.5 10.0	56 min. 58 min. 80 min.	Died after removal from jar in apnea; heart still beat, but respiration never resumed; autopsy done immediately	...	Marked engorgement of sinusoids; early degenerative changes in central portion of lobule
3	1.9	19	8.5 10.7 13.0	2 hr. 3 hr. 11 hr.	Near asphyxiation; limp but conscious; respiration moist; not disturbed by anoxia; killed immediately after removal from jar	...	No noteworthy degenerative changes seen
4	2.0	20	11.2	9½ hr.	Restless at times; respiration often jerky and irregular; seemed in good condition on removal from jar; killed 1 hr. later	...	Definite evidence of necrosis, most pronounced around central veins and spreading outward into lobule in irregular patterns; cells in areas of degeneration showed affinity for eosin; in some areas cell outlines completely lost
5	1.4	14	9.3	1½ hr.	Died in bell jar	...	Marked engorgement of sinusoids; early degenerative changes around central vein; cell outlines often lost; vacuoles in cytoplasm
6	2.7	27	12.5	1 hr.	Died in bell jar	...	Early changes
7	2.5	25	11.0	7 hr.	Respiration rate rapid; died in bell jar; autopsy done immediately	...	Widespread necrosis; large areas staining deeply with eosin; cell outlines in many places had disappeared; nuclei in these areas pyknotic
8	2.2	22	11.6	1 hr.	Died 6 hr. after removal from bell jar	...	Marked engorgement of sinusoids; early degenerative changes with loss of cell boundaries and pyknotic nuclei
9	1.6	16	11.0	9½ hr.	Killed 1 hr. after removal from jar	3.2	No outstanding deviation from normal
10	1.7	17	10.5	9½ hr.	Killed 1 hr. after removal from jar	0.5	Definite areas of degeneration; loss of cell boundaries; pyknotic nuclei and polymorphonuclear leukocytes seen among the necrotic cells
11	1.8	18	11.0	9½ hr.	Killed 1 hr. after removal from jar	3.1	Slight early degenerative changes
12	2.1	21	10.5	8 hr.	Died in bell jar	...	Extensive degeneration; marked engorgement of blood vessels; pyknotic nuclei; loss of cell boundaries
13	2.2	22	11.0	1 hr.	Died just after removal from jar	...	Marked engorgement of blood vessels; early degenerative changes with vacuolation of cells and loss of cell boundaries
14	2.4	24	10.0	8½ hr.	Died 5½ hr. after removal from jar	...	Extensive degeneration and hemorrhage
15	1.5	15	10.6	4 hr.	Died in bell jar	...	Marked engorgement of sinusoids and early degenerative changes
16	2.5	25	10.5	6¾ hr.	Stormy course; removed from bell jar early to prevent death; killed 24 hr. later	1.5	Extensive areas of degeneration and necrosis
17	1.6	16	11.0	8½ hr.	Killed 24 hr. after removal from jar	1.0	Widespread degenerative changes and necrosis

\* Among the 17 animals with hyperthyroidism 14 showed evidence of hepatic damage varying from slight early changes to extensive necrosis. There were 9 deaths among these animals.

before they could be removed from the bell jar, 2 shortly after removal and 1 six hours later. The 4 other deaths occurred after varying periods of anoxia.

*Pathologic Examination of the Liver.*—With 2 exceptions the animals killed were put to death about an hour after termination of the anoxia.

The control rats without exception showed no lesions of the liver (table 2). Fourteen of the 17 hyperthyroid rats had such lesions. As might be expected, the lesions in animals that died or were killed after

TABLE 2.—*Experiments on Anoxia with Normal Rats\**

Control Rat	Anoxia		Comment	Hepatic Glycogen, Gm. per 100 Cc.	Histologic Examination of Liver
	Oxygen, per Cent	Duration			
1	11.0	40 min.	Killed 1½ hr. after removal from bell jar	2.5	No essential deviation from normal
	9.3	38 min.			
	5.9	50 min.			
	8.7	42 min.			
	8.7	37 min.			
2	11.0	40 min.	Killed 1½ hr. after removal from bell jar	...	No essential deviation from normal
	9.3	38 min.			
	5.9	50 min.			
	8.7	42 min.			
	8.7	37 min.			
3	7.5	7.5 hr.	Lethargic but not especially distressed; not killed		
4	11.2	9½ hr.	Killed 1 hr. after removal from bell jar	3.2	No essential deviation from normal
5	11.5	6 hr.	Killed 1 hr. after removal from bell jar	...	No essential deviation from normal
	11.2	9½ hr.			
6	11.2	9½ hr.	Killed 1 hr. after removal from bell jar	4.4	No essential deviation from normal
7	11.3	9½ hr.	Killed 1 hr. after removal from bell jar	3.5	No essential deviation from normal
8	11.2	9½ hr.	Killed 1 hr. after removal from bell jar	4.7	No essential deviation from normal
9	11.5	9½ hr.	Slept quietly through-out; killed 1 hr. after removal from bell jar	2.7	No essential deviation from normal

\* There were no deaths among the 9 control rats, and examination of the liver revealed no degenerative changes.

short exposures were not advanced; they consisted of fatty changes, vacuolation of cells and engorgement of blood vessels.<sup>10</sup> In the animals exposed for longer periods the degenerative changes were usually severe and widespread. Outstanding lesions of the liver are shown in figures 3 to 10 and may be contrasted with the normal hepatic cells of a control animal shown in figures 1 and 2. In 2 instances the rats were killed twenty-four hours after being removed from the bell jar, and the lesions

10. As stated previously, in some of the earlier experiments both controls and thyroxin-treated animals were killed after short exposures. Since the changes in the thyroxin-treated rats were slight, longer periods of anoxia were used in later experiments.

of the liver found in 1 of them (rat 16) are shown in figures 7 and 8. This animal, as shown in table 1, tolerated the low oxygen atmosphere poorly and had to be removed after approximately seven hours. The general condition for several hours thereafter was not satisfactory, the animal appeared weak and the respiration was rapid. The next morning, however, the condition seemed essentially normal.

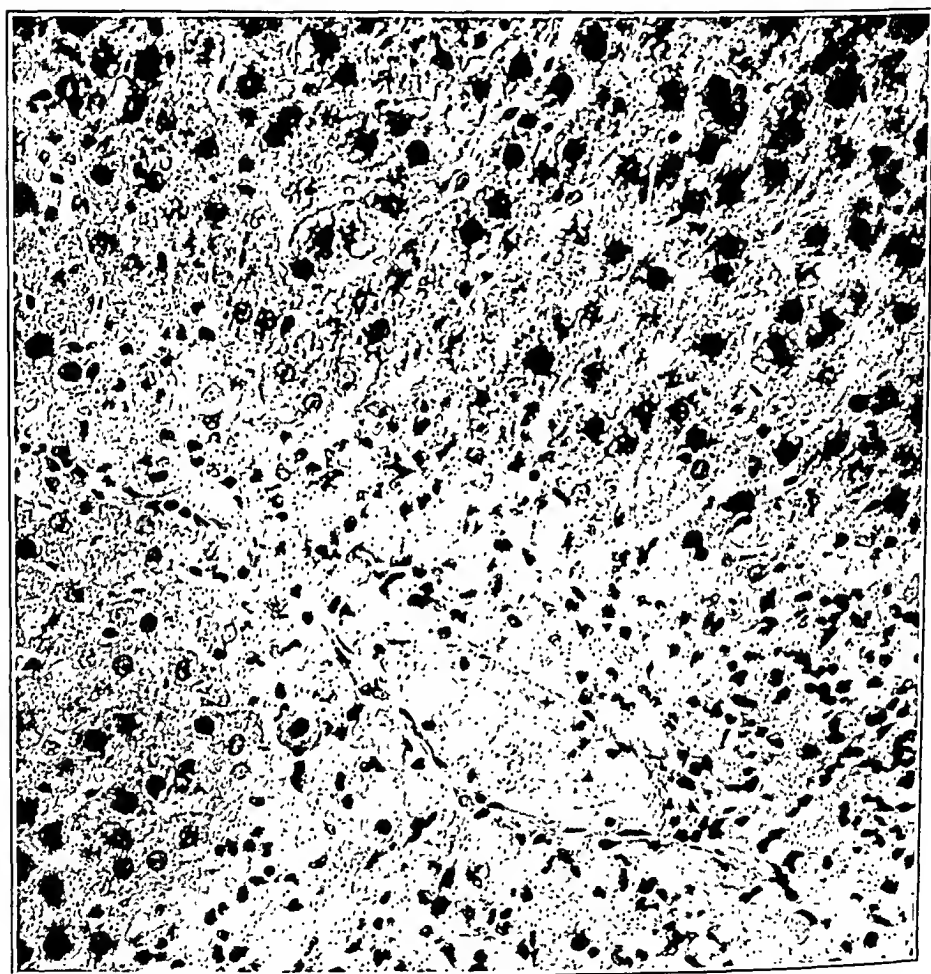


Fig. 8.—Higher magnification ( $\times 300$ ) of the section shown in figure 7, presenting the area of degeneration in detail.

*Hepatic Glycogen.*—Lewis and associates,<sup>11</sup> in their recent studies on the role of the adrenal cortex in acute anoxia, confirmed the earlier work of Evans,<sup>12</sup> showing that hepatic glycogen tends to increase in rats

11. Lewis, R. A.; Thorn, G. W.; Koepf, G. F., and Dorrance, S. S.: The Rôle of the Adrenal Cortex in Acute Anoxia, *J. Clin. Investigation* **21**:33, 1942.

12. Evans, G.: The Effect of Low Atmospheric Pressure on the Glycogen Content of the Rat, *Am. J. Physiol.* **110**:273, 1934; The Adrenal Cortex and Endogenous Carbohydrate Formation, *ibid.* **114**:297, 1936.

exposed to low atmospheric pressure. Lewis and his co-workers noted, however, that prior to this increase, during the first twelve hours of exposure to low concentrations of oxygen, there is a fall in the glycogen level. Our periods of anoxia all came within the twelve hour period, and as might be expected in view of the observation of Lewis and his associates, the glycogen level in these rats, both thyroxin-treated and normal animals, was low. It is interesting that although our controls and

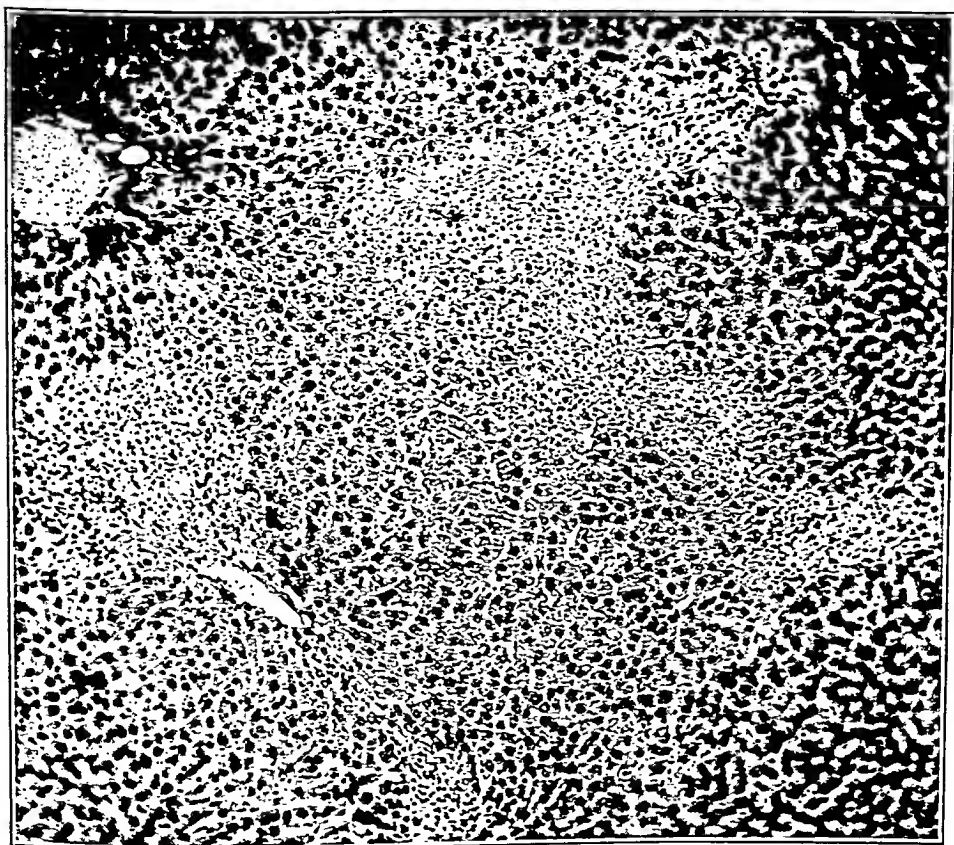


Fig. 9.—Section of the liver stained with hematoxylin and eosin, taken from rat 10, which went through a preliminary period of administration of thyroxin followed by anoxia of nine and a half hours' duration. The concentration of oxygen was 10.5 per cent. Numerous areas of necrosis are shown. (Magnification,  $\times 100$ .)

our hyperthyroid animals both showed low levels of hepatic glycogen, damage to the liver occurred only in the latter group. This is in harmony with recently published observations by us,<sup>6b</sup> which showed that the low level of hepatic glycogen in hyperthyroid rats was not the essential factor in their increased susceptibility to chloroform poisoning.

*Body Temperature.*—In the control animals during exposure to anoxia there was a drop in body temperature averaging 2.2 C. (4 F.). The rats with hyperthyroidism similarly exposed showed in most instances some drop in temperature; this averaged 1.2 C. (2.2 F.), or a degree (C.) less than the drop in the controls. In 4 of the hyperthyroid animals there was a slight rise in body temperature, of about 0.5 C. (0.9 F.), and in 1 there was a rise of 1.8 C. (3.2 F.). In the 2 hyperthyroid animals

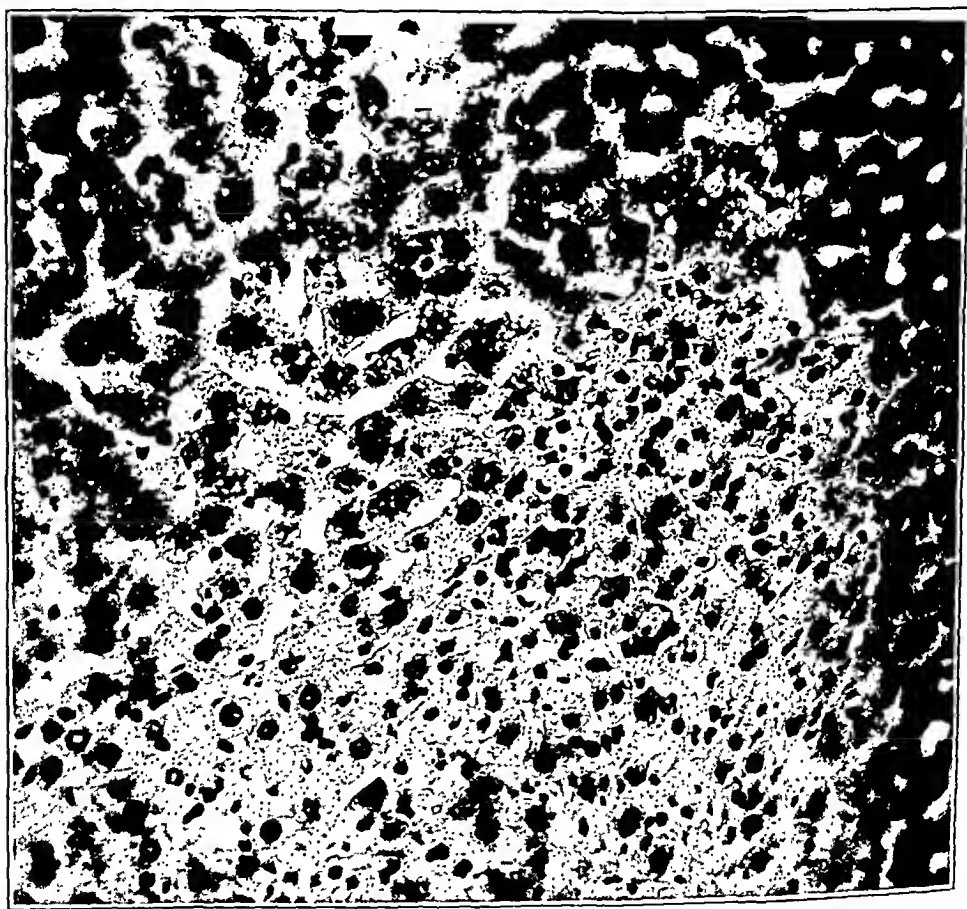


Fig. 10.—Higher magnification ( $\times 300$ ) of the section shown in figure 9, presenting one area of degeneration in greater detail.

that were not killed until twenty-four hours after removal from the bell jar, there was a slight rise in temperature after the termination of the anoxia.

#### COMMENT

On the basis of these experiments it seems evident that anoxia is capable of producing degenerative changes in the liver in animals with hyperthyroidism; this finding may in some instances explain the acute

lesions found in the livers of patients dying of hyperthyroidism.<sup>13</sup> The problem is of clinical importance, since anoxia is a hazard to which hyperthyroid patients are often exposed.<sup>14</sup> This is especially true after operations on the thyroid gland, when tracheal obstruction, pulmonary edema or some other complication may interfere with efficient aeration of the lungs. Also, according to Hartman,<sup>15</sup> hyperpyrexia, a constant feature of the thyroid crisis, may in itself contribute to anoxia.

#### SUMMARY

Rats given injections of crystalline thyroxin for two to three weeks in doses of 0.1 mg. daily in general remained in good condition, although they showed clinical signs of hyperthyroidism and when they were killed the hepatic glycogen level was found to be low. They showed no degenerative lesions of the liver.

On exposure to atmospheres containing low concentrations of oxygen, in 14 of 17 hyperthyroid animals varying degrees of hepatic injury developed. There were 9 deaths among the total of 17 rats.

In a group of control normal rats similarly exposed to low concentrations of oxygen hepatic lesions did not develop. There were no deaths in this group.

It is suggested that in some instances the acute lesions found in the livers of patients dying of hyperthyroidism may be the result of anoxia.

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13. Weller, C. V.: Hepatic Pathology in Exophthalmic Goiter, *Ann. Int. Med.* 7:543, 1933. Beaver, D. C., and Pemberton, J. deJ.: The Pathologic Anatomy of the Liver in Exophthalmic Goiter, *ibid.* 7:687, 1933. Shaffer, J. M.: Disease of the Liver in Hyperthyroidism, *Arch. Path.* 29:20 (Jan.) 1940. Kerr, W. J., and Rusk, G. Y.: Acute Yellow Atrophy Associated with Hyperthyroidism, *M. Clin. North America* 6:445, 1922. Lichtman, S. S.: Liver Function in Hyperthyroidism, with Special Reference to the Galactose Tolerance Test, *Ann. Int. Med.* 14:1199, 1941. Boyce, F. F., and McFetridge, E. M.: Studies of Hepatic Function by the Quick Hippuric Acid Test: II. Thyroid Disease, *Arch. Surg.* 37:427 (Sept.) 1938.
14. Haines, S. F., and Boothby, W. M.: Oxygen Treatment with Special Reference to Treatment of Complications Incident to Goiter, *Am. J. Surg.* 7:174, 1929. Schnedorf, J. G.; McClure, R. D., and McGraw, A. B.: Rationale and Use of Oxygen in the Postoperative Treatment of Hyperthyroidism, *Surg., Gynec. & Obst.* 72:26, 1941. Cole, W. H., and Brunner, R.: Anesthesia in Thyroidectomy for Thyrotoxicosis, *ibid.* 70:211, 1940.
15. Hartman, F. W.: Lesions of the Brain Following Fever Therapy: Etiology and Pathogenesis, *J. A. M. A.* 109:2116 (Dec. 25) 1937.

# DELAYED SPLENIC RUPTURE: A CLINICAL SYNDROME FOLLOWING TRAUMA

REPORT OF FOUR CASES WITH AN ANALYSIS OF ONE HUNDRED AND SEVENTY-SEVEN CASES COLLECTED FROM THE LITERATURE

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AND

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DETROIT

Acute conditions within the abdomen remain among the most important and at the same time most complicated of all surgical syndromes. In the present state of war interest in traumatic injuries is increased, with good reason. The type of acute abdominal injury to be discussed in this paper has not received the attention that its frequency warrants. This syndrome differs from other examples of acute abdominal conditions in that a latent period varying from a matter of hours to days or even weeks may follow the original trauma. During this latent period the patient may complain of an associated injury, such as a fracture of a long bone or a rib; he may be troubled by vague abdominal pain, or he may actually be almost symptom free. Then in typical cases a gradually developing splenic hematoma suddenly ruptures and the patient presents signs of collapse, shock and severe anemia; if operation is not promptly performed, he dies. This condition, with its original injury, insidious latent period and fulminating secondary hemorrhage, is the condition of delayed splenic rupture.

Injury to the spleen is probably the most common of all serious subcutaneous abdominal injuries. Bronaugh (1935) reported that injury to the spleen occurs in 33.3 per cent of subcutaneous injuries involving abdominal viscera. Mazel (1932) reported a frequency of 30 per cent, and Wright and Prigot (1939) found the incidence to be 47.6 per cent. Injury to the liver was next in frequency, with a 28.6 per cent incidence. Trauma accounts for rupture of the normal spleen in almost every case. It may be caused by falls and from automobile, motorcycle and bicycle accidents, as well as by other types of violence. Accidents occurring in aeroplanes and in swiftly moving tanks may cause splenic rupture in wartime.

Delayed splenic rupture accounts for a far higher percentage of all splenic lacerations than is commonly realized. Thus it is seen in

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From the Division of General Surgery, Henry Ford Hospital.

table 1 that from 5 to 40 per cent of all ruptures are of the delayed type, the average incidence being 14 per cent. Since McIndoe's review in 1932, sporadic reports have cited the infrequency of this condition. In reality the ratio of delayed to immediate hemorrhage is about 1 to 6. Werthmann, of Frankfort on the Main, Germany, had 4 cases in two years, while Orator (1939) saw 2 examples of the syndrome in Schmieden's clinic in one year. In this condition there is the advantage—seldom utilized as yet—that during the latent period operation may be performed, or at least the condition diagnosed and the patient observed expectantly. Splenic hemorrhage, immediate or delayed, is rapidly fatal

TABLE 1.—*Ratio of Delayed to Total Splenic Ruptures in Reported Series*

Author	Year	Splenic Ruptures		Delayed Ruptures as Percentage of Total Cases
		Delayed	Total	
Bailey (London Hospital).....	1894-1926	6	32	19
Connors.....	1928	3	32	9
Foster and Prey.....	1940	1	20	5
Rousselot and Illyne.....	1941	1	17	6
Zabinski and Harkins.....	1942	4	10	40
Total.....		15	111	14

TABLE 2.—*Collected Series of Cases of Delayed Splenic Rupture*

Author	Year	Number of Cases
Nast-Kolb.....	1912	9
Schlegel.....	1926	16
Herfarth.....	1926	25
Quénu.....	1926	22
Kment.....	1930	42
Becker.....	1932	45
McIndoe.....	1932	46
Werthmann.....	1932	52
Hageney.....	1939	70
Müller.....	1940	75
Zabinski and Harkins.....	1942	177

unless immediate operation is performed, and is therefore one of the gravest abdominal emergencies requiring surgical intervention.

#### ANALYSIS OF LITERATURE

Since no other review has included more than 40 per cent of the reported cases, it was felt that a collective study of this important syndrome was in order. In 1912 Nast-Kolb collected 9 cases of delayed splenic rupture. Other reviews are shown in table 2. Data on the following cases are not available: Séjournet, 1933; Popoviciu and Mihaileanu, 1933; Bronaugh, 1935; Dorronsoro Montes, 1936; Mash-takov, 1936; Bergan, 1939; Vasilkovan, 1939; Krivonosov, 1939; Montanari, 1941 (2 cases); Monod, 1931, and Spiridonovič. 1932.



The present analysis is based on 66 new cases collected from the literature as well as 4 cases of patients treated at the Henry Ford Hospital. Our cases are divided under the following heads: cases 1 to 46, cited by McIndoe (1932); cases 47 to 80, additional cases cited by Müller (1940); cases 81 to 107, incomplete or untraceable reports; cases 108 to 111, 4 personal cases; cases 112 to 177, 66 previously uncited cases collected from the literature.

*Cases 1 to 46.*—The review by McIndoe (1932) represents the most complete report on delayed splenic rupture which has appeared in the English language up to the present time. The discussion of cases therein is so complete that we have not reanalyzed them in the present paper.

*Cases 47 to 80.*—Müller (1940) collected 80 cases of delayed splenic rupture from the literature. Three of these are duplications, and 2 of them (those of Herfarth and of Stamm) are doubtful. This article, however, with its 75 definite cases, still represents the most extensive review outside of our own. Thirty-four of Müller's cases are not included in our own series or are not cited by McIndoe. They include those of Abasbridze, Becker, Borchard, Brogsitter, Burgerhout, Cadénat, Fuchs, Gohrbandt, Haffter, Henderson, Heuser, Hochwalter, Junkermann, Kauff, Kofranek (2 cases), Ledderhose, Mannheim, Marx, Mastador, Molnár, Moore and Alexander, Monod, Patey, Ramon, Rolle, Roughton, Schachnowitz, Schmidt, Schubert, Soison, Stefanini, Turnagallie and Wildanker.

*Cases 81 to 107.*—These represent reports with data insufficient for analysis, or for which the reference could not be checked. In this list are 27 cases, including those of Bailey (1927), 5 cases; Bergan (1939), Bronaugh (1935), Connors (1928), 3 cases; Dorronsoro Montes (1936), Kempf (1923), Krivonosov (1939), Mashtakov (1936), Monod (1931), Montanari (1941), 2 cases; Pietrzikowski (1920), Popoviciu and Mihaileanu (1933), Pou, 2 cases; Rousselot and Illyne (1941), Séjournet (1933), Spiridonovič (1932), Vasilkovan (1939), Wiederkov (1920) and Zubkov.

*Cases 108 to 177.*—These include the cases of 4 patients seen at the Henry Ford Hospital and 66 additional cases collected from the literature. None of the latter are included in McIndoe's report. These 70 cases form the chief basis for our analysis and are listed hereinafter.

#### PERSONALLY OBSERVED CASES

CASE 108.—W. C., a man aged 36, was struck with a milk bottle in the region of the left kidney. Two days later he had some abdominal pain, relieved by a bowel movement. Six days after the injury the patient was seized with a severe pain in the left shoulder, with collapse and generalized severe abdominal pain. He vomited a small amount. The temperature, the pulse and the respirations were normal.

Findings included tenderness in the upper part of the abdomen and a white blood cell count of 12,200. A preoperative diagnosis of pancreatitis or perforated peptic ulcer was made. At operation the abdomen was found to be filled with blood. A 3 cm. laceration on the diaphragmatic surface of the spleen was felt. Splenectomy was done, and recovery ensued.

CASE 109.—C. McM., a man aged 43, was struck over the left shoulder and knocked down by a barrel falling 14 feet (4.25 meters). He felt weak momentarily. It was found that he had a fracture of the eighth rib on the left side in the mid-axillary line. For the next few days his temperature rose to 101 F. No cause for the fever could be found. Five days after the initial injury, while straining at the stool, he began to feel weak and perspired profusely. In five hours the patient was blanched and had pain only over the site of the fracture. There was no abdominal pain or tenderness. The hemoglobin content dropped from 14.6 to 11.8 Gm. per hundred cubic centimeters. A diagnosis of intra-abdominal hemorrhage was confirmed at operation, at which time a fragmented spleen was removed. The patient was pulseless during the splenectomy but responded to blood transfusions. He left the hospital in good condition.

CASE 110.—O. L., a man aged 49, was admitted to the hospital one day after an automobile-train wreck. He presented marked splinting of the entire abdomen, especially in the lower half. There was also tenderness in the region of the left kidney. The blood pressure was 120 systolic and 68 diastolic. The pulse and the temperature were normal. During the next few days the abdomen became softer, although it always maintained slight rigidity. Seven days after the injury severe abdominal pain, cold sweat, pallor and delirium developed. The blood pressure was not obtainable. The pulse rate was 130, and the temperature was normal. The patient received 1,000 cc. of blood, and splenectomy was done. On the second postoperative day bronchopneumonia developed, and the patient died on the third day after operation.

CASE 111.—O. M., a man aged 48, had an automobile accident on Nov. 18, 1940, after which he remained in bed because he felt tired. During this time he had a little abdominal pain on the left side. Four and one-half days after the injury he became suddenly gravely ill, with collapse, weak pulse and fall in blood pressure. The white blood cell count was 20,700, and the hemoglobin content was 11.5 Gm. per hundred cubic centimeters. Abdominal exploration was done at once by one of us (H. N. H.). Free blood was present in the peritoneal cavity, associated with a 2.5 cm. laceration of the splenic capsule and a hematoma under the capsule at the site of rupture. Splenectomy was done, and the patient was given a transfusion during the operation. Postoperatively bronchoscopic examination was made for aspiration pneumonia, and thrombophlebitis developed in the right leg, for which continuous injection of heparin was used. The patient was discharged from the hospital in good condition.

#### REPORTED CASES

A series of 66 reported cases of traumatic subcutaneous rupture of the spleen with delayed hemorrhage is presented and forms an essential element of the statistical analysis later in this article. The following facts are tabulated: author, date of the report, age of the patient, sex, initial injury, latent period, type of onset of secondary

1. This case has previously been reported *in extenso* by one of us (H. N. H.).

hemorrhage, symptoms, signs, associated lesions, pathologic changes, result, complications, preoperative diagnosis and comment. Cases on which data are insufficient or not obtainable have been mentioned on the previous pages. The cases reviewed by McIndoe (1932) are not included in this list, which represents reports with details adequate for analysis.

CASE 112 (Richardson, 1923).—The patient, a boy aged 12 years, fell off a bicycle. Six days later he had pain in the left side of the abdomen and the left shoulder with sudden onset. Operation revealed a ruptured spleen with much free blood in the peritoneal cavity. Splenectomy was followed by recovery.

CASE 113 (Heymann, 1927).—After an automobile accident, a physician suffered abdominal pain, which rapidly improved. Nine days later he had pain in the shoulder and the abdomen with sudden onset. Operation revealed a tear at the hilus of the spleen; this organ, however, was not removed because of shock. Death ensued.

CASE 114 (Bailey, 1927).—A workingman aged 40 was hit in the upper part of the abdomen by a pole. He fainted but soon recovered sufficiently to report to the hospital, where he was examined and told to report the next day. This he did not do, because he felt better. Five days later he suffered sudden collapse with evident signs of internal hemorrhage; splenectomy was done a few hours later with recovery.

CASE 115 (Martens, 1927).—A physician received an injury in a motorcycle accident. Two days later he had abdominal pain, distention and rigidity. A diagnosis of peritonitis was made, and at operation the lower third of the spleen was found to be torn off. An accessory spleen was also removed. The patient recovered.

CASE 116 (Wilson, 1927).—A man aged 55 was struck by a falling log. He had no pain in the abdomen after the second day. Nine days after the accident abdominal pain developed, but there was no tenderness and no rigidity. The temperature was normal; the pulse rate was 100. The patient died in thirteen hours without benefit of operation. Autopsy revealed rupture of an infarct of the spleen and amyloid degeneration of the liver.

CASE 117 (Nelson, 1928).—A man aged 61 was thrown against a wall by a cow. He was treated for fractured ribs. Thirteen hours later he became pale. The pulse rate was 120, and there was dulness in both flanks. The spleen was ruptured, and splenectomy for tears at the hilus and the costal surfaces was done. The patient recovered.

CASE 118 (Berndt, 1929).—A woman aged 23 was struck in the left upper quadrant of the abdomen by her husband. Thirteen days later the patient had gradual onset of two attacks of abdominal pain and dizziness. Pallor and tenderness in the left hypochondrium were noted. The temperature was 37.5 C. (99.5 F). The pulse was weak, and the rate was 125. There was intra-abdominal bleeding, and splenectomy was done; a 2 cm. tear near the hilus was discovered at operation. The patient recovered.

CASE 119 (Kment, 1930).—A man aged 21 was hit in the left side of the abdomen. Fifty hours later there was sudden onset of abdominal pain and pain in the left shoulder, associated with vomiting and collapse. The abdomen was rigid and tender, and a diagnosis of splenic rupture was made. At operation 1.5

liters of blood was found in the abdominal cavity; there was a rupture of the splenic capsule. Recovery took place after splenectomy.

CASE 120 (Kment, 1930).—A man aged 25 was in an automobile accident. He was admitted to the hospital, and his condition improved. However, on the tenth day in the hospital he had rapid onset of pain in the abdomen and left shoulder, accompanied by vomiting. The abdomen was tender, distended and boardlike. There was dullness in the flanks. Operation revealed a splenic rupture and tear of the capsule. The patient recovered after splenectomy.

CASE 121 (Dawson-Walker, 1931).—A woman aged 34 received a blow to the left side of the back. Two weeks later the patient experienced gradual onset of severe epigastric pain and pain in the shoulder. No collapse took place. There was no pallor, no shifting dullness in the flanks and no rigidity. The temperature was 97.6 F., the pulse rate 120, and the respiratory rate 28. The patient was operated on and was found to have internal hemorrhage from a ruptured subcapsular hematoma. Death from shock occurred the first day after splenectomy.

CASE 122 (Hochmiller, 1931).—A man aged 22 fell flat on his back. Twenty-four hours later pain in the abdomen developed, associated with weakness, nausea, collapse, anemia, distention and shifting dullness. The temperature was 37.7 C. (99.86 F.) and the pulse rate 120. A diagnosis of ruptured liver or spleen was made. There was laceration of the capsule, and splenectomy was followed by a wound infection. Recovery occurred. A blood count taken one year later was entirely normal.

CASE 123 (Wagner, 1931).—A man aged 25 was struck with a hammer in the left hypochondrium. Two days later he complained of pain in the abdomen. There was no collapse. Dullness was present in the upper part of the abdomen. The temperature was 37 C. (98.6 F.). A diagnosis of ruptured peptic ulcer was made, and a hilar laceration was found at operation. Recovery took place after splenectomy.

CASE 124 (Bumm, 1931).—A woman aged 23 fell downstairs twice. Twelve days later she had to remain in bed one day. Forty-one days after the accident abdominal pain and shock developed rapidly, and the patient vomited. She was pulseless and had a distended and tender abdomen. Anemia was present. The presence of blood on vaginal puncture led to the diagnosis of a ruptured ectopic pregnancy. Operation revealed a subcapsular hematoma and tear of the entire convex surface of the spleen. The patient recovered.

CASE 125 (Oudard and Guichard, 1932).—A man aged 30 fell into a dry-dock. Four days later he experienced generalized abdominal pain, tenderness and rigidity in the left hypochondrium. Dullness was present in the left flank. The temperature was 38.6 C. (101.48 F.), and the pulse rate was 100. The patient was operated on, and intraperitoneal hemorrhage, probably splenic, was discovered. A subcapsular and perisplenic hematoma was found. The patient died of anuria due to a transfusion reaction.

CASE 126 (Oudard and Guichard, 1932).—A youth aged 20 fell off a bicycle. Twenty-four hours later pain in the left shoulder, epigastrium and left hypochondrium developed, associated with tenderness and rigidity. A splenic rupture was diagnosed and a subcapsular hematoma was found at operation. The patient recovered.

CASE 127 (Oudard and Guichard, 1932).—A boy aged 16 fell 4 meters and suffered a fracture of a rib on the left side and of the right radius and a transverse rupture of the spleen. Forty hours later pain developed in the upper part

of the abdomen and collapse occurred. There was subcostal rigidity and tenderness, low blood pressure and dulness in the splenic area. The temperature was normal, and the pulse rate was 90. The patient recovered after splenectomy.

CASE 128 (Oudard and Guichard, 1932).—A youth aged 20 was struck by an assailant's fist under the left costal margin. Five hours later subcostal pain and collapse developed, with rigidity. The temperature and the pulse were normal. At operation a subcapsular hemorrhage with no free blood in the peritoneal cavity was found. Recovery ensued.

CASE 129 (Kohn, 1932).—A man aged 48 fell while drunk. On the fifth day colicky abdominal pain developed, associated with nausea, pallor, abdominal distention and tenderness. The temperature was 37.3 C. (99.14 F.), and the pulse was weak. A diagnosis of acute appendicitis was made. At operation a 4 cm. capsular tear of the spleen was discovered, and there was 1,000 cc. of blood in the peritoneal cavity. The patient recovered after operation. Bronchitis was a complication in this case.

CASE 130 (Werthmann, 1932).—A boy aged 13 fell while ice-skating. Eight hours later extreme pallor, and restlessness developed. The patient was operated on, and a tear of the convexity of the spleen was found. He recovered.

CASE 131 (Werthmann, 1932).—A man aged 31 was involved in a motorcycle accident. Twenty-seven hours later extreme pallor developed, and there was dulness in the left upper quadrant of the abdomen but no distention. When the patient was operated on the spleen was found to be in three parts, and there was a hematoma of the mesentery. The patient recovered after operation.

CASE 132 (Werthmann, 1932).—A girl aged 4 was run over by an automobile. Forty-six hours later acute abdominal pain developed, associated with dulness and tenderness in the left upper quadrant of the abdomen. There was a fracture of the humerus. On operation two lacerations of the spleen were noted; these divided the spleen into three parts. The patient recovered after operation.

CASE 133 (Werthmann, 1932).—A woman aged 29 was in a motorcycle accident. Ninety hours later she experienced abdominal pain and vomiting. Examination revealed dulness in the left side of the abdomen and pallor. A tear of the convexity of the spleen was discovered at operation. The patient recovered.

CASE 134 (Bertrand, 1933).—A youth aged 18 was involved in a motorcycle accident. He had slight abdominal pain, but thirty-six hours later severe abdominal pain developed, associated with syncope, sweating and extreme pallor, but there was no abdominal tenderness. The pulse rate was 160. Operation revealed an intraperitoneal hemorrhage. The spleen was in two pieces, one being in the pelvis. Recovery occurred in spite of pulmonary complications.

CASE 135 (Kirschner, 1933).—A man aged 28 fell 2.5 meters, fracturing the left ulna. Hematuria developed, and eight days later, while straining at the stool, he experienced pain in the left upper quadrant of the abdomen and collapsed. The hemoglobin content of the blood was 80 per cent. The pulse was poor. Operation revealed a splenic rupture, a 6 cm. tear of the convexity and 1,500 cc. of blood in the peritoneal cavity. The patient recovered.

CASE 136 (Modezejewski, 1933).—A woman aged 26 fell downstairs. She remained in bed only three days. On the twelfth day after the accident sudden collapse developed, with abdominal pain and rigidity, vomiting, a pulse rate of 136, and a temperature of 35.8 C. Operation revealed a capsular tear of the spleen with a subcapsular hematoma. Splenectomy was followed by recovery.

CASE 137 (Dodd, 1934).—A man bumped his left lower ribs during a fall. After a free interval of twelve hours severe pain in the upper part of the abdomen, with vomiting and diarrhea, began to develop. The temperature was 100 F. and the pulse rate 120, and there was tenderness over the cecum; hence a diagnosis of acute appendicitis was made. The operation, which required only fifteen minutes, was accompanied by shock and revealed a laminated perisplenic hematoma. Splenectomy was followed by recovery.

CASE 138 (Dodd, 1934).—A woman aged 56 struck her chest on a chair during a fall. She continued to do her housework, although she did not feel well. Two days later, with a slow onset, abdominal pain, weakness and dyspnea developed. Shifting dullness in the flanks and rigidity, tenderness and dullness in the left upper quadrant of the abdomen were noted. The temperature was 99 F., the pulse rate 120 and the hemoglobin content of the blood 55 per cent. A diagnosis of ruptured spleen was made. Operation was accompanied by shock and revealed a laceration of the spleen. Splenectomy was followed by recovery.

CASE 139 (Meltzer, 1935).—A young man fell 4 meters. Two days later he became ill suddenly, with pain in the upper part of the abdomen, and collapse ensued. Operation revealed a splenic rupture. Splenectomy was followed by recovery.

CASE 140 (Moulonguet and Suire, 1935).—A man aged 37 fell off a motorcycle. A basal fracture of the skull was diagnosed. He had abdominal tenderness for a few days. After nine days pain in the left upper quadrant of the abdomen, pain in the left shoulder and shock developed. There was dullness in both flanks, and the pulse rate was 180. The patient was operated on, and internal hemorrhage and a subcapsular splenic hematoma were revealed. Splenectomy was done, and the patient recovered.

CASE 141 (Hunter, 1935).—A man aged 33 fell from a motorcycle on his abdomen and left shoulder. A progressively enlarging abdomen, making the patient unable to walk, became apparent. There was severe abdominal pain, and anemia and fluid waves were noted. The peritoneal cavity was explored twenty days after the accident, and 9 pints (4.25 liters) of fluid blood was removed; the spleen was not removed because bleeding had ceased.

CASE 142 (Gardiner, 1935).—A youth aged 19 fell from a fence. He remained in bed for six days, during which time he had only one bowel movement. On the seventh day at breakfast the patient was seized with severe abdominal pain and pain in both shoulders and with faintness. The temperature was 97 F., and the pulse rate was 92. Rigidity and tenderness over the abdomen were noted, and there was increased splenic dullness. There was a laceration of the long axis. Splenectomy was done, and the patient recovered.

CASE 143 (Schmid, 1935).—A woman aged 38 fell and struck the left splenic region. Twenty-eight days later, while washing clothes, she became suddenly sick, with severe abdominal pain, and collapse occurred. A fractured left rib was discovered. There was a question of a tubal pregnancy in this case. Splenectomy was performed for a subcapsular hematoma, and recovery took place.

CASE 144 (Wenger, 1936).—A girl aged 19 fell down a flight of stairs. She had pain on standing straight, pain in the upper part of the abdomen and weakness. Seven days after the accident the patient suddenly went into collapse and had pain in the left side of the abdomen and left shoulder. Shifting dullness, and fluid waves were noted. The temperature was 99.6 F., and the pulse rate was 144. She was treated for a broken rib. The diagnosis of a probable ruptured

spleen was made. At operation a rupture of the anterior surface was found, for which splenectomy was done. Because of the shortness of the splenic pedicle a portion of the tail of the pancreas had to be included in the ligature. Recovery ensued.

CASE 145 (Sertoli, 1936).—A man aged 49 was hit by a motorcycle. There was slight contracture of the abdomen the first few days, but on the ninth day the patient became gravely ill with generalized abdominal pain, collapse, anemia and generalized rigidity. The pulse rate was 100. The diagnosis of a perforated gastric ulcer was made. At operation a large splenic laceration was found, and splenectomy was done. The patient died.

CASE 146 (Laporte, 1936).—A man aged 35 was struck and pinned under a car. He vomited after the accident. After two days sharp pain developed in the left hypochondrium and he went into sudden collapse. The pulse rate was 120. A ruptured spleen was found at operation, and there were 4 liters of blood in the peritoneal cavity and a tear near the hilus. The patient died in shock after the operation.

CASE 147 (Laporte, 1936).—A man aged 32 suffered a fall. Two days later sharp periumbilical pain and pain in the left shoulder suddenly developed, associated with nausea and tenderness and dulness in the splenic region. The pulse rate was 100. A ruptured spleen was revealed on operation, and there was 1.5 liters of blood in the abdominal cavity. A subcapsular hematoma was present. Recovery took place after operation.

CASE 148 (Mouchet and Léger, 1936).—A man aged 32 fell from a roof. Three days later he had sudden pain in the left upper quadrant of the abdomen, pain in the shoulder and nausea, followed by collapse. There were tenderness and rigidity in the left upper quadrant of the abdomen and slight distention. The temperature was 37.6 C. (99.68 F.), and the pulse rate was 120. There were a fractured eleventh rib and a left hemothorax. A ruptured spleen was diagnosed. Subcapsular hemorrhage and tear of the diaphragmatic surface of the organ were discovered at operation, and there was 1.5 liters of free blood in the peritoneal cavity. Phlebitis developed, but the patient eventually recovered.

CASE 149 (De Monie, 1937).—A youth aged 20 fell off a motorcycle, striking the left side of his chest and flank. Two days later the patient went into sudden collapse, with vomiting, low blood pressure, pain in the epigastrium and left shoulder and tenderness in the epigastrium and left hypochondrium, which in twenty-one hours became localized in the left upper quadrant of the abdomen. There was dulness in the region of the liver and the left iliac fossa. The temperature was 37.2 C. (98.96 F.) and the pulse rate 120. A ruptured spleen with subcapsular hematoma and a hilar tear was found at operation. Splenectomy was followed by recovery.

CASE 150 (Bonfield, 1937).—A man aged 27 was in an automobile that was struck by a streetcar. He appeared pale after the accident. Two days later he went into collapse, with severe abdominal pain, chiefly in the left hypochondrium. The spleen was found to be ruptured and was three times its normal size. A subcapsular hematoma and a tear in the convexity of the spleen were found. Postoperatively the hemoglobin content of the blood was 60 per cent and the white cell count 43,000. The patient recovered.

CASE 151 (Hohenwallner, 1938).—A man aged 55 had a fall and was hospitalized for five days. Four months later he became suddenly sick with abdominal pain. Pallor and abdominal dulness, distention and tenderness were noted on exam-

ination. A diagnosis of perforated peptic ulcer was made. There was a tear of the upper pole of the spleen 3 cm. deep. The patient had had malaria twenty years previously. He recovered after operation.

CASE 152 (Lange, 1938).—A man aged 45 was hit in the left side of the abdomen. Pleurisy developed, followed on the fourth day by cold sweats and pain in the left shoulder and abdomen, associated with rigidity and tenderness. A ruptured spleen was found at operation. After a follow-up period of nine months recovery was considered complete.

CASE 153 (Wright and Prigot, 1939).—A woman aged 36 was in an automobile accident. She had pain in the left upper quadrant of the abdomen for a few days. Two weeks later there was a sudden onset of pain in the left side of the chest and the left shoulder, with nausea and fainting. The blood pressure was 90 systolic and 74 diastolic. The red cell count of the blood was 2,900,000, the hemoglobin content 65 per cent and the white cell count 6,100. The patient was short of breath. An abdominal tap revealed blood. A diagnosis of acute pancreatitis was made. A ruptured spleen was discovered at operation. Splenectomy was followed by recovery.

CASE 154 (Wright and Prigot, 1939).—A woman aged 22 sustained a fracture of the eighth rib on the left side in an automobile accident. The patient had recurrent symptoms indicative of slow onset of hemorrhage. Two weeks after the accident pain in the left side of the chest and left shoulder and general malaise developed. After three days she again became asymptomatic, remaining so until the day before her admission to the hospital, three weeks after the accident. At the time of her admission the hemoglobin content of the blood was 45 per cent, the red cell count 2,700,000 and the white cell count 21,300. The temperature, pulse and respirations were normal. The original diagnosis of pneumonia was changed to that of splenic rupture because of abdominal symptoms of increasing severity. Splenectomy was performed, and the patient recovered.

CASE 155 (Blocker, 1939).—A man aged 34 felt a sharp evanescent pain in the left upper quadrant of the abdomen while lifting a heavy beam. One and one-half days later, while at the stool, the patient was seized with pain in the left flank. Pallor and generalized abdominal tenderness were noted. The blood pressure was 90 systolic and 60 diastolic, and the pulse rate was 128. There was dullness in both flanks. A diagnosis of probable ruptured spleen was made. The spleen was found hanging from the pedicle by a few shreds of capsule, and a subcapsular hematoma was present. Recovery took place after operation.

CASE 156 (Delannoy, 1939).—A man aged 45 fell off a bicycle. After the accident he had slight persistent pain in the left upper quadrant of the abdomen. On the eighth day, on arising from bed, he was suddenly seized with a sharp pain in the left upper quadrant and collapsed. There were tenderness and abdominal distention. The temperature was 37.9 C. (100.22 F.) and the pulse rate 90. There were ecchymoses at the umbilicus. At operation a ruptured spleen with laceration of the superior pole and parenchymatous hemorrhage was found. There was 1.5 liters of blood in the abdomen. The patient recovered after splenectomy.

CASE 157 (Webb, 1939).—A boy aged 8 years was struck by a puck during a hockey game. On the fourth day, while he was putting on his coat, pain in the left side and classic symptoms of ruptured spleen suddenly developed. At operation a laceration of the outer surface and two subcapsular hematomas were found. The patient recovered after splenectomy.



CASE 158 (Orator, 1939).—A youth aged 17 was hit in the left upper quadrant of the abdomen. Eight days later he was suddenly seized with abdominal pain, associated with shock, weakness, pallor and a hemoglobin content of 50 per cent. Operation disclosed an intra-abdominal hemorrhage. Splenectomy was performed, and recovery ensued.

CASE 159 (Orator, 1939).—A man aged 38 was struck in the left upper quadrant of the abdomen in an automobile accident. He was asymptomatic until three days later, when some abdominal pain developed. On the fifth day the pain suddenly became worse, so that he was unable to stand up. The hemoglobin content of the blood was 70 per cent and the white cell count 17,000, and there was tenderness in the left upper quadrant of the abdomen. A diagnosis of splenic rupture was made. Operation revealed that the capsule was separated from the entire convex surface of the spleen and that there was 1,500 cc. of free blood in the peritoneal cavity. Splenectomy was followed by recovery.

CASE 160 (Kufferath, 1939).—A woman aged 24 walked to the hospital after being hit in the left upper quadrant of the abdomen. She had pain in the back and a slow onset of symptoms of internal hemorrhage. At operation 1,500 cc. of free blood was removed. The patient recovered after splenectomy.

CASE 161 (Segal and Jaffe, 1939).—A woman aged 42 fell downstairs but continued with her housework until the twelfth day after the accident, when she suffered increasing pain in the left side of the abdomen associated with vomiting. Within twenty-four hours the patient was in shock. The blood pressure was 50 systolic and 0 diastolic. The hemoglobin content of the blood fell from 62 to 42 per cent and the red cell count from 3,400,000 to 2,900,000. The white cell count was 12,200. The pulse rate ranged from 100 to 130. At operation a ruptured spleen with a tear of the capsule and tamponade by clots was found. Splenectomy was done, and the patient recovered.

CASE 162 (Piulachs, 1939).—A man aged 46 fell 12 feet (3.65 meters). On the twelfth day pain in the shoulder, collapse, pallor and swelling below the ribs developed over a period of seven hours. The temperature was 37.5 C., and the pulse rate was 100. A cyst of the spleen was found on operation, and there were hemorrhage and fragmentation. A laceration of the kidney was also revealed. The patient died.

CASE 163 (Zschau, 1939).—A man aged 30 was hit by a motorcycle on the left side. He had some pain on the left side on expiration, and his left elbow was fractured. Seven days after the accident rapid collapse occurred, accompanied with abdominal pain. Operation revealed a 6 cm. tear in the spleen, with infarction and with 750 cc. of free blood in the peritoneal cavity. Splenectomy was followed by recovery.

CASE 164 (Foster and Prey, 1940).—A boy aged 13 tripped over a fence, striking his chest and abdomen. He had no immediate symptoms other than mild colic. On the third day he was seized with pain in the left side of the abdomen and vomited. Examination revealed dullness in the left flank, with rigidity. The hemoglobin content of the blood was 80 per cent, the red cell count 3,500,000 and the white cell count 12,500. The temperature was 99.6 F., and the pulse rate was 85. A diagnosis of delayed splenic rupture was made. At operation bleeding of the superior pole of the spleen was found, and tamponade was done. A wound disruption with secondary hemorrhage and an intestinal obstruction necessitated two additional operations, but the patient eventually recovered.

CASE 165 (Prestow, 1940).—A man aged 43 fell 102 feet (31 meters). He fractured eight ribs on the left side, the first lumbar vertebra, the left tibia and the left os calcis. There was slight rigidity in the left upper quadrant of the abdomen. On the fifteenth day he was suddenly seized with severe pain in the left upper quadrant of the abdomen and left side of the chest. Collapse ensued, and abdominal rigidity and tenderness were noted. The pulse rate was 140. At operation intra-abdominal hemorrhage, probably splenic, was discovered. There was also a subcapsular hemorrhage, and the pedicle of the spleen was torn. The patient recovered after splenectomy.

CASE 166 (Steenrod, 1940).—A lineman aged 20 fell 30 feet (9.4 meters) after contact with a live wire. He was severely burned and suffered a fracture of the tenth rib on the left side, with pneumothorax. Nine days later severe epigastric pain developed, accompanied with vomiting and collapse. The blood pressure was 70 systolic and 0 diastolic. Fluid waves were noted in the abdomen. The temperature was 99.6 F., and the pulse rate was 128. A spleen enlarged to three times its normal size and a tear of the lower pole of the spleen were found at operation. Evisceration with obstruction in the splenic fossa subsequently developed, and the patient died on the twenty-ninth day.

CASE 167 (Cheeves, 1940).—A youth aged 17 sustained an injury while playing football. He presented slowly developing, recurrent symptoms of splenic rupture and after two days went into shock. At operation a subcapsular hematoma and a large laceration across the middle of the spleen were found. Splenectomy was followed by recovery.

CASE 168 (Davis, 1940).—A woman aged 38 was in an automobile accident. She received a blow over the left side of the chest, followed by pain in the left upper quadrant of the abdomen and the left shoulder. Four days later she had an attack of generalized abdominal pain, felt nauseated and collapsed. The pulse rate was 132. The blood pressure was 118 systolic and 78 diastolic, the hemoglobin content of the blood 25 per cent and the white cell count 12,600. There was general abdominal tenderness, with dullness in both flanks. The spleen was found to be disrupted on operation. The patient died ten hours postoperatively.

CASE 169 (Müller, 1940).—A railroad engineer aged 40 was struck on the left side when his bicycle fell on top of him, but was able to go to work. Six hours later he went into a state of collapse, with pain, tenderness and rigidity in the left upper abdominal quadrant. The white cell count of the blood was 15,200 and the hemoglobin content 85 per cent, and there were signs of fluid in the abdomen. Operation revealed a tear in the splenic capsule with coagula in the substance of the organ. Splenectomy was followed by pneumonia and death on the fifth day.

CASE 170 (Müller, 1940).—A laborer aged 38 was well for thirty-six hours after a fall. With a slow onset over a twelve hour period abdominal pain developed, accompanied with tenderness in the left upper quadrant of the abdomen, pallor and weakness. The temperature was 38 C. (100.4 F.), the white blood cell count 18,000 and the blood pressure 120 systolic and 85 diastolic. A diagnosis of acute appendicitis preceded operation. A tear at the hilus of the spleen with free blood in the peritoneal cavity was found. Splenectomy was followed by evisceration and peritonitis, and death occurred on the eighth day.

CASE 171 (Müller, 1940).—A woman aged 40 fell downstairs, striking the left side very hard. Except for occasional pain in the shoulder she was well for two years, after which abdominal pain, weakness and tenderness in the left upper quadrant of the abdomen suddenly developed. A diagnosis of peritonitis led to

operation, at which free blood was found in the peritoneal cavity coming from a thick-walled hemorrhagic cyst in the left upper quadrant of the abdomen and attached to the spleen. Splenectomy led to recovery.

CASE 172 (Deaver, 1941).—A man aged 24 suffered fractures of the nose, left scapula, left clavicle and left third and fourth ribs when an automobile in which he was riding overturned. There was transient pain in the left upper quadrant of the abdomen. On the twenty-third day severe abdominal pain suddenly developed, followed by collapse. Slight anemia, abdominal tenderness and fluid waves were noted. The temperature was normal, and the pulse rate was 108. Roentgenograms showed elevation of the left dome of the diaphragm. Splenectomy revealed that the anterior surface of the spleen was torn. The patient recovered.

CASE 173 (Frank, 1941).—A youth aged 17 was injured while playing football. He had no definite complaints until two days later, when pain in the left side of the abdomen and left shoulder developed, followed by collapse. On his admission to the hospital the temperature was 100 F. and the pulse rate varied from 80 to 90. At operation an intra-abdominal hemorrhage was revealed. The spleen was torn completely through, the tear extending into the splenic pedicle. The patient recovered.

CASE 174 (Fey and Turow, 1941).—A man aged 50 was struck over the left side of the chest in a fight. On the sixth day pain in the epigastrium and the left shoulder developed, and the patient vomited. Eight hours later he went into shock. No attempt was made to elicit Ballance's sign. The temperature was 96 F., and the pulse was feeble. The pulse rate was 140; the respiratory rate, 36. At operation a subcapsular rupture of the spleen was found. The patient recovered.

CASE 175 (Lommen, 1942).—On June 6, 1936 a boy aged 14 collided with another boy while chasing a ball, the other boy's head striking him in the abdomen. He was at once brought to the hospital. The red blood cell count was normal; the white cell count, 18,600. There were some generalized abdominal pain and tenderness. Two days after the accident the patient was discharged with a diagnosis of contusion of the spleen, and three days later he returned to school. On June 13, seven days after the accident, abdominal pain, tenderness and rigidity, especially in the left upper quadrant, suddenly developed, accompanied with faintness, sweating, pallor and a compressible pulse. A splenectomy, performed at once after a blood transfusion, revealed a laceration 7 cm. long in the region of the hilus and much blood in the peritoneal cavity. The patient recovered.

CASE 176 (Roettig, Nusbaum and Curtis, 1943).—A male college student was admitted to the hospital shortly after an automobile accident as a result of which he lost consciousness. He was not in shock. He remained in the hospital, and on the eighth day sat up in a chair. The red cell count had fallen from 5,060,000 the day of admission to 3,420,000 the day he sat up. That evening he had sudden severe abdominal pain, with signs of shock. The red cell count was 2,600,000 and the white cell count 35,000. Operation performed after a blood transfusion revealed a ruptured subcapsular splenic hematoma, which was treated by tamponade and suture. Recovery ensued.

CASE 177 (Roettig, Nusbaum and Curtis, 1943).—An 18 year old boy entered the hospital with severe abdominal pain, nausea, vomiting and weakness of twelve hours' duration. Five weeks previously he had been struck in the left upper quadrant of the abdomen in an explosion. The temperature was now 100 F., the pulse rate 110, the respiratory rate 20 and the blood pressure 90 systolic and 50 diastolic. The

red cell count was 3,900,000 and the white cell count 22,400. The patient had severe pain with generalized abdominal rigidity and tenderness. At operation, a perisplenic hematoma was found with an associated laceration of the spleen. The laceration was sutured and the splenic fossa packed. The patient had an uneventful recovery.

#### ANALYSIS OF CASES

*Age.*—The greatest number of injuries occurs during the third decade of life, and the number remains relatively constant through the following three decades. This observation is at variance with the opinion of those who say that splenic injury is incurred most frequently in the younger age group. The youngest patient was 4 years old; the oldest, 61 years. In McIndoe's series most injuries occurred between the ages of 15 and 50 years.

*Sex.*—Fifty-five of the patients in this series were males; 15 were females, producing a ratio of 3.5 to 1. The ratio given in a previous large collection of cases was 9 to 1.

TABLE 3.—*Type of Accident Producing Delayed Splenic Rupture*

Falls.....	25
Automobile accidents.....	10
Assault and battery.....	8
Motoreyele accidents.....	8
Bicyele accidents.....	5
Run over by automobile.....	2
Blows by objects.....	6
Football injuries.....	2

*Initial Injury.*—The normal spleen is small and fixed in a protected position. Subcutaneous injuries to the spleen are usually the result of severe or moderately severe trauma. Robitshek was of the opinion that while slight trauma may produce these injuries, it is usually of a degree sufficient to produce other accompanying injuries. However, the damage to the spleen is of course slight, because temporary recovery usually takes place in a short time. Severe trauma, such as that due to a fall from a great distance, or to being pinned under a car, was responsible for 19 cases. Moderately severe trauma, such as is caused by an automobile accident, a fall or a blow by object or fist, accounted for 44 cases. In 5 instances the trauma was slight, being due to a fall while the patient was ice-skating or walking, to bumping the left side or to falling over a low fence. In only 1 case was the rupture spontaneous—the case of a man who felt a stitch in his side while lifting a heavy beam. This was probably the result of direct violence to the spleen by muscular compression. Injury directed to the left hypochondrium is markedly infrequent. It has also been noted that direct violence usually causes parenchymal and capsular lacerations, while indirect violence often is responsible for hilar tears. Table 3 presents the frequency of each type of injury.

Foster and Prey reported automobile accidents as the responsible factor in 70 per cent of 20 cases of immediate hemorrhage. Bailey (1927) found street accidents to be more important than falls (14 and 10 cases respectively out of a total of 32 cases of splenic rupture of all types), even though his report partially covered a period before the automobile (1894 to 1926). In another series of splenic ruptures of all types Connors reported that in 22 cases the trauma was caused by the patient's being struck by a vehicle and in 7 it was due to a fall. In 3 of Connors' cases there was a free interval of at least twenty-four hours. These occurred in a series of 32 subcutaneous ruptures of the spleen of all types, an incidence of 9 per cent. In the present series of cases of delayed hemorrhage automobile accidents were causative in 18 per cent, while falls accounted for 38 per cent. It appears that automobile accidents are more apt to produce immediate splenic hemorrhage, while falls are the most common cause of delayed rupture of the organ.

*Latent Period.*—The latent period, so termed by Baudet, a period of symptomatic relief following the injury, denotes the interval from the cessation of bleeding following the initial injury to the onset of secondary hemorrhage. The mechanisms of hemostasis involved will be discussed under pathogenesis. The duration varied from several hours to three months, but secondary hemorrhage occurred most often before the end of the first week. McIndoe stated that it took place most frequently from the third to the ninth day. Hageney (1939) found the interval in from 50 to 60 per cent of his cases to be less than one week, in 20 per cent from one to two weeks, and in the remainder less than thirty-nine days, with the exception of 1 patient who had an interval of six months. Orator (1939) presents a case of splenic rupture occurring two years after the patient was hit in the left side. The extremely long interval gives rise to doubt as to any connection between the original injury and the subsequent rupture. Schmid (1935) stated that no cases of delayed splenic rupture occurred with an interval of more than nineteen days. This is not strictly accurate, for in the present series there were 8 patients in whom bleeding began after twenty days. Furthermore, McIndoe's classic article cited 1 case with an interval of six months. Kallius (1942) stated that in 80 per cent of cases the capsule ruptures within the first week and in 20 per cent within the second or third week. Müller's third case (1940), with a two year latent period (case 171), seems to be quite authentic, however, the thick-walled, head-sized hemorrhagic cyst indicating the chronic course. Table 4 notes the frequency of the duration of the latent period.

It has been thought that a diagnosis of ruptured spleen could be made during the latent period and splenectomy performed before secondary

hemorrhage took place. Delannoy (1939) distinguished two clinical types of secondary hemorrhage: 1. Rupture with retarded symptoms, which corresponds with a perisplenic hematoma. With this type the patient continues to suffer pain in the left hypochondrium or shoulder. The temperature or pulse rate may be elevated. Gastrointestinal disorders occur. There may be persistent tenderness, rigidity or dulness. Roentgenograms may show a paralyzed diaphragm with a subjacent shadow. 2. Splenic ruptures with retarded hemorrhage, corresponding to intrasplenic or subcapsular hematoma. With this variety symptoms appear suddenly after a completely asymptomatic period.

*Symptoms and Signs During Latent Period.*—In the present series pain was the outstanding symptom during the latent period. It varied from abdominal discomfort to pain localized in the left upper quadrant, colicky or persistent. It was localized to the left upper quadrant in

TABLE 4.—*Length of the Latent Period Between Injury and Delayed Splenic Rupture*

Latent Period	Cases
5-48 hours.....	11
2-6 days.....	22
7-11 days.....	15
12-16 days.....	7
21 days.....	1
23 days.....	1
27 days.....	1
28 days.....	1
35 days.....	1
41 days.....	1
3 months.....	1
2 years.....	1

only 4 instances. Two patients were unable to stand erect because this position initiated the pain. Rigidity and tenderness during the first few days after the accident were uncommon findings. In only 1 case was there definite enlargement of the abdomen. Systemic signs of bleeding, such as pallor, malaise, faintness, sweats and weakness were noted but were uncommon. One patient complained of pain on the left side of the lower part of the chest without a broken rib. One of our patients had an unexplained rise of temperature to 101 F. Definite evidence of a perisplenic hematoma during the latent period was not present in any case. McIndoe, however, was able to note a few instances of this variety of injury in which the following signs were present: fulness and an increase in splenic dulness, slight pallor, weakness, dizziness or occasional fainting. Costal breathing and an accelerated pulse rate were also reported. Quénu (1926) felt that a diagnosis of ruptured spleen could be made during latency on a person who after receiving trauma to the left hypochondrium presented a good general state but had some sensitivity in that area, a slight but persistent rigidity and a slight elevation in temperature. Oudard and Guichard (1932) stated

that two types of symptoms were present as a result of bleeding, with the accompanying peritoneal irritation: (1) pain in the splenic region with rigidity and increased splenic dullness, and (2) immobilization of the left lobe of the lung without pleural or pulmonary signs.

*Pathologic Changes in Subcutaneous Rupture.*—Obviously, the pathologic changes in this condition vary with the stages of the process, which are the initial injury, the latent period and the period of secondary hemorrhage.

Four types of initial injury are responsible for the progression of the symptoms. They are: (1) minor parenchymal contusions or capsular lacerations; (2) intrasplenic and subcapsular hematoma; (3) perisplenic hematoma with an initial parenchymal and capsular laceration; (4) tears of the pedicle.

The first type is purely theoretic, because the symptoms provoked are not severe. Minor injuries tend to form blood cysts or to heal spontaneously and do not warrant exploration. Undoubtedly the majority of intrasplenic and subcapsular hematomas remain as such, or they may continue to bleed, subsequently producing capsular ruptures and free peritoneal hematoma. The changes incident to a perisplenic hematoma will be discussed. It is rather difficult to see in what way hilar tears may be responsible for secondary hemorrhage. All of the authors whose cases are included in this report have cited instances of spontaneous rupture of a supposedly previously normal spleen. Zschan (1939) reported a delayed rupture of a leukemic spleen. Ruptures of malarial spleens are frequent, and Maes and Rives (1941) state that one thirtieth of all deaths in the malaria-infested area about Calcutta are due to such an accident.

In the present series, as in McIndoe's, intrasplenic bleeding occurred before rupture of the capsule in over 50 per cent of the cases. In a few cases there was an associated laceration of the capsule with a perisplenic hematoma. A combination of subcapsular hematoma and capsular laceration was present in only 14 of the 57 cases with available data. Lacerations were the most frequent operative finding. The violence of the secondary hemorrhage caused disruption of the spleen in 5 cases and detached the spleen in 1 case. Free or clotted blood in the peritoneal cavity was absent in only 1 case, an instance of subcapsular hematoma without a capsular tear. Table 5 summarizes the operative findings.

The pathogenesis of the latent period can be interpreted in various ways. This is an interesting field for speculation, and the following theories and observations have been offered:

1. Temporary hemostasis produced by the state of shock. Hemorrhage is concomitant with the injury. Should the hemorrhage from a splenic injury be severe enough to produce shock, temporary cessation

of bleeding is affected by the same processes as are seen in shock from other causes. This theory is more directly applicable to cases of immediate hemorrhage, in which it is frequently noted that improvement follows the initial shock stage.

2. Hematoma under tension. Intrasplenic bleeding may be made to cease by an enlarging hematoma which exerts compression on the contused pulp.

3. Theory of subcapsular hematoma. Demoulin expressed the belief that when bleeding is more or less abundant the capsule is detached and forms a sort of hood in which clots collect. Then from any cause whatever, even from distention, the capsule ruptures, producing intraperitoneal hemorrhage.

TABLE 5.—*Pathologic Changes in Delayed Splenic Rupture*

Changes in the Spleen	Cases
Tear of convexity.....	26
Tear of diaphragmatic surface.....	2
Tear of costal surface.....	1
Tear of superior pole.....	1
Tear of inferior pole.....	1
Multiple lacerations.....	3
Subcapsular hematoma.....	18
Multiple subcapsular hematoma.....	1
Complete decapsulation.....	1
Laminated perisplenic hematoma.....	1
Disruption of spleen.....	5
Spleen torn from pedicle.....	1
Torn pedicle.....	4
Tear through spleen into pedicle.....	1
Rupture of an infarct.....	1
No free blood in peritoneal cavity.....	1
Combined subcapsular or parenchymal hematoma and laceration of spleen or pedicle.....	14

4. Formation of clots at the laceration (Werthmann). Clots in various stages of organization have been observed rather frequently at the site of the laceration. The extrasplenic clot is detached readily even by minimal effort.

5. Tamponade by omentum (Mannheim, Routier, Nast-Kolb). Plugging of the laceration by omentum is believed to be one of the most effective means for arresting hemorrhage.

6. Tamponade by stomach, colon or adhesions (Oudard and Guichard). The distended stomach or colon may seal the laceration. Abnormal perisplenic adhesions may do the same. These organs help keep the clot in the laceration under tension.

7. Theory of perisplenic hematoma (Delannoy, McIndoe). The spleen is surrounded by a potential space bounded on all sides by organs which are easily displaced. Hemorrhage from the injury surrounds the spleen, elevates the diaphragm and displaces the splenic flexure of



the colon and the parietal walls. Adhesions are formed, uniting the various organs and producing an enclosure which does not permit peritoneal flooding.

8. Theory of threshold of hemorrhage (Laporte). The organism can tolerate some hemorrhage, but at a certain threshold signs of hemorrhage appear. This theory is borne out by those cases that have an onset prolonged over several hours.

Kiment in 1930 reviewed 42 cases of delayed rupture and found that in 8 of these there was self tamponade with blood clots and in 3 with adhesions. In Herfarth's series there were 8 cases of tamponade by clots, 1 of tamponade by omentum and 2 of tamponade by adhesions. Hageney (1939) collected 70 cases of delayed splenic rupture, in 75 per cent of which the condition was due to rupture of a subcapsular hematoma and in the remainder to temporary blockage of the tear with clots, omentum or other organs.

*Secondary Hemorrhage.*—The symptoms and signs of splenic hemorrhage are those of peritoneal and diaphragmatic irritation, shock and hemorrhage. It is a matter of no small surprise to have an onset of severe pain or shock following minor exertion or apparently coming on spontaneously. In 4 cases the onset occurred while the patient was straining at stool. In 1 patient it occurred when he was arising from bed, and in another, while she was washing clothes. Frequently it occurred when no unusual stress was present.

The usual abrupt onset of secondary hemorrhage initiates a characteristic train of symptoms. It is ushered in with pain in the abdomen, chest or shoulder. The abdominal pain, varying in severity, may be general or localized to the left side of the abdomen, left hypochondrium, epigastrium, upper part of the abdomen or periumbilical region. In only 1 patient was abdominal pain absent. Pain in the left shoulder (Kehr's sign) was present in 19 of 68 recorded cases, and pain low in the left side of the chest was the presenting symptom in 3 cases. Kroh (1939) doubted the importance of pain in the left shoulder as a sign of splenic rupture. In a series of 7 cases of splenic trauma personally observed during the previous three years, this author did not once see a positive example of this sign. Tenderness was generalized or localized to the left upper quadrant of the abdomen. In only 1 instance (Dodd's first case, our case 137) was it over the cecum, and this patient was the only one who had diarrhea. Dodd's explanation of this phenomenon is as follows: Bleeding from the lacerated spleen irritates the splenic flexure and descending colon into contraction, thus causing the diarrhea. Later, this segment of bowel becomes paralyzed by aseptic peritonitis. The ensuing partial intestinal obstruction is followed by distention and tenderness of the cecum in the right iliac fossa. Nyström (1918) reported 3 cases of immediate splenic rupture

in which intestinal distention was severe. Rigidity, when present, was more often general than local. In 3 cases with pain, rigidity and tenderness were absent. McIndoe expressed the opinion that rigidity in abdominal contusions, not limited to the injured part, is of diagnostic significance and is a clear indication for laparotomy.

Nausea or vomiting occurred in 17 cases. Diarrhea and constipation were each present once.

Collapse, or shock resulting from hemorrhage, soon follows or may be an initial sign. Shock was noted in 31 instances and syncope in 4. The accompanying signs of hemorrhage were noted as follows: Low blood pressure was recorded in only 8 cases; in 3 it was normal at the onset. Acute anemia was recorded 18 times. Pallor was present in 28 cases. Weakness, sweating, restlessness and air hunger also were noted. Fifteen patients had a white cell count ranging from 12,000 to 43,000. In 1 case there was a normal white cell count. The symptoms of shock and hemorrhage are indistinguishable clinically, except in those patients who improve after the initial shock but have symptoms of hemorrhage later. Furthermore, the two conditions need not be differentiated, since they are treated in a similar manner (Harkins). Berger stated that 51.8 per cent of patients with a ruptured spleen die within one hour as the result of hemorrhage. Seven of McIndoe's patients died before anything could be done for them.

The presence of blood in the peritoneal cavity may be determined by percussion. Dulness limited to the splenic region or in the left flank was noted in 23 cases. A fluid wave was obtained in 7 instances. Ballance's sign, fixed dulness in the left flank due to the enlarging hematoma and shifting dulness in the right flank, was present in 1 case. This sign should be present at some time during the course of the disease. Abdominal distention was observed 9 times.

The temperature was most frequently normal or subnormal. Slight elevations are not uncommon, but temperatures above 100 F. are distinctly rare. The pulse is usually rapid and poor in quality. In 10 instances the pulse rate was below 90. Respiration is rapid and costal in type.

Two signs are frequently cited in the literature:

Ballance's sign, shifting dulness in the right flank and fixed dulness in the left, indicates a large amount of free blood as well as a large hematoma. Bailey (1927) stated that there are many references to this sign in the literature but that the consensus seems to be that it is so rarely present as to be almost valueless. Connors (1928) noted it in only 1 of 32 subcutaneous splenic ruptures. Rousselot and Illyne noted it in 5 of 17 cases. In our series it was also noted only once.

Kehr's sign is referred pain in the left shoulder due to stimulation of the phrenic nerve. Bailey (1927) found this sign quite evident

in certain of his cases of ruptured spleen. Rousselot and Illyne noted it in 4 of 17 cases. Kehr's sign was present in at least 28 per cent of our cases and was a much more useful diagnostic help than Balance's sign.

*Diagnostic Aids.*—Leukocytosis and the anemia of hemorrhage have already been discussed. Roentgen examination has proved of value in establishing a diagnosis in a few cases. Webb (1939) reported the following changes in a typical case: (1) increased density in the left upper quadrant of the abdomen; (2) elevation of the left side of the diaphragm; (3) displacement of the stomach to the right side; (4) free fluid between loops of the intestine. In 1 of our cases with continuing hemorrhage the diaphragm was markedly elevated. In another case we observed recently the colon was displaced medially and a shadow marking a mass was present in the left upper quadrant of the abdomen. Bancroft (1942) noted a separation of the air shadow in the stomach when the patient was in an inverted position. Bancroft's patient, a boy aged 11 years, was in the hospital for three days after receiving a blow to the left side. The temperature was 100 F.; the hemoglobin content of the blood was 70 per cent, and the patient felt quite weak. Bancroft gave the patient barium sulfate by mouth, put him in the Trendelenburg position and observed a mass in the region of the spleen displacing the stomach. Operation revealed a lacerated spleen with a massive hematoma. Splenectomy was performed. This is one of the few cases in which operation was done to forestall a secondary rupture of the spleen. Burke and Madigan (1933) administered colloidal thorium dioxide (24 cc.) to a patient with a ruptured liver and spleen after operation, and were able to outline the ruptures in these organs. One half of the usual dose is used. They thought this procedure might be of value when physical signs are obscured, as by alcoholism. However, this procedure requires about four hours and is not without danger.

Paracentesis has been recommended by Wright and Prigot. In 13 out of 15 cases, including 2 cases of delayed hemorrhage, the result of the test proved positive, i. e., blood was obtained. Two "false positive" results were obtained on patients with ruptured kidneys. The tap may have to be repeated if the patient continues to show signs of internal bleeding and the first tap gives a negative result. Vaginal puncture has been used to obtain peritoneal blood. Bumm (1931) used this procedure on a patient with a preoperative diagnosis of ruptured ectopic pregnancy.

Peritoneoscopic examination has not been used, but it may be of value in doubtful cases.

*Associated Lesions.*—Other lesions resulting from the initial injury may obscure the underlying splenic trauma. Fractured ribs on the left side were noted in 11 instances. McIndoe noted this feature in

10 of his 46 cases. Intrathoracic hemorrhage and pneumothorax on the left side were seen once. Contusion and laceration of the kidney and a hematoma of the mesentery were also present. Fractures of other bones were rare and are unimportant from a diagnostic standpoint. De Monie found fractured ribs in 10 per cent of his cases, while lesions of the left kidney accounted for 12 per cent. In 5 per cent there was accompanying damage to the lungs. This frequency of fractured ribs with splenic rupture should make one suspicious of the underlying splenic injury.

*Preoperative Diagnosis.*—A correct diagnosis of splenic bleeding was made in 20 cases. Internal hemorrhage was diagnosed in an additional 12 cases. The following mistaken diagnoses were made: ruptured ectopic pregnancy in 3 cases; perforated peptic ulcer, peritonitis and acute appendicitis, twice each; acute pancreatitis and pneumonia, once each. In 24 cases a preoperative diagnosis was not presented.

*Results of Operation.*—Difficulty in diagnosis and watchful waiting are the causes for the high mortality. Kallius (1942) points out that the prognosis of secondary rupture of the spleen is less favorable than that of primary rupture. The patient remembers that the first abdominal crisis soon passed off and believes that the new attack will do likewise. Thus time is lost, and he does not seek medical help sufficiently soon. Although all of the symptoms of primary splenic hemorrhage (increased splenic dullness and progressive anemia, local tenderness, pain in the left shoulder, retraction of the testicle on the left side, vagus pulse, increasing pain when the patient lies on the back, and shock going on to collapse) may not be present, at least some of them are usually evident, and the patient is usually clear as to the determining injury. Kallius believes that in this last regard a history of evanescent shock associated with hyperesthesia of the left phrenic nerve is especially significant. It has been stated that in ordinary splenic rupture the average interval between admission and the time of operation is twelve hours. Those who continue to keep patients with ruptured spleens under observation for a protracted period fail to realize the seriousness of this surgical emergency. We believe that all patients with ruptured spleen for whom a diagnosis can be made during the latent period should have the benefit of immediate surgical treatment. Whenever a definite diagnosis cannot be made but the suspicion of a splenic rupture is entertained, it is best to keep the patient at rest in bed for at least two weeks to lessen the possibility of delayed hemorrhage. During this time enemas are forbidden. Food is not withheld. Blood counts should be made several times daily, and progress roentgenograms of the abdomen should be taken at intervals.

In 62 cases in which the result was mentioned, 53 patients recovered and 9 died, a gross mortality of 14.5 per cent. Fifty-seven patients had

undergone splenectomy; 3 had tamponade and in 4 the spleen was not removed. Six patients died after splenectomy, a mortality of 10.5 per cent.

McIndoe reported an operative mortality of 27 per cent. Seven patients died before anything could be done. Of 9 patients that were not operated on, 8 died.

In untreated splenic rupture the mortality ranges from 77 to 100 per cent. Berger reported a 93 per cent fatality rate in 220 cases of splenic rupture of all types in which no operation was done. The mortality rate reported by Watkins was 100 per cent, by Connors 100 per cent and by Lemerenz 77 per cent. Zschau (1939), in a report on a probable case, stated that the patient bled secondarily on the fifth day but recovered with conservative management.

Regarding the type of operation, splenectomy is the only procedure to be used. Tamponade is uncertain, and bleeding may not be controlled. Splenorrhaphy carries a mortality of 5 to 20 per cent. Dretzka, reporting a preponderance of gunshot and stab wounds, was enthusiastic about repair and tamponade, and he had a mortality of 20 per cent among 10 patients. Tamponade has only a single indication—the patient who is a very poor risk and for whom splenectomy would be fatal. Splenectomy, however, offers the quickest means of stopping hemorrhage and with modern methods of prophylaxis and treatment of shock with plasma and serum has extended indications.

The technic of splenectomy has been admirably covered recently by Cole, and a new technic has been described by Rives for splenectomy in the presence of difficult adhesions. Several special features, however, are worthy of mention. Bailey (1923) stated that the pedicle is found to be friable only in cases of delayed hemorrhage. His explanation of this point is that the pedicle after being surrounded by mildly irritating blood itself becomes edematous and undergoes degeneration. It is far safer to employ individual ligatures applied by transfixion close to the spleen than a mass ligature, which is more likely to cut. Michels (1942) pointed out the fact that the position of the splenic artery is as variable as that of the cystic artery. When preliminary ligation or clamping of the artery is done it is occasionally difficult to find the vessel, because its position may be prepancreatic, intrapancreatic, retropancreatic or suprapancreatic. The main splenic artery divides into its two terminal branches from 1 to 7 cm. from the hilus, and in most instances there are two hili.

*Complications.*—Dehiscence of the abdominal wound has been seen frequently. Bailey reported that in 4 of 32 cases in which the paramedian incision was used the wound burst open. Connors noted 3 cases of severe suppuration of the abdominal wall following splenectomy for rupture. The cause for what is called suppuration is undoubtedly

digestion of the edges of the wound by pancreatic enzymes which result from injury to the pancreas. This may also be a factor in disruption. Studies of vitamin C, plasma protein and diastatic activity were not done on any of the patients with disruption. Injury to the pancreas, of course, does not always cause digestion of the abdominal wall or separation of the edges of the wound. In 1 of the patients in the present series damage to the tail of the pancreas was not followed by any complication. In the present series the following complications occurred: 2 wound disruptions, 1 severe wound infection, 2 cases of intestinal obstruction, and 1 each of pleural effusion and pneumonia. There were also 2 cases of phlebitis and 1 of anuria from a transfusion reaction.

*Late Results.*—The late results of splenectomy are chiefly anemia and leukocytosis which persist for months. Lymphoid hypertrophy may occur (Pfeiffer and Smyth), and a persistent enlargement of the superficial glands may be noted.

#### SUMMARY AND CONCLUSIONS

All of the available reports concerning delayed splenic rupture have been collected. The total of 177 cases, while it represents over two and one-half times as many instances of this syndrome as have been reported in any previous summary, still does not represent the true frequency of this condition. Traumatic rupture of the normal spleen is the most common serious subcutaneous abdominal injury. Delayed splenic rupture (the *hémorragie en deux temps* of the French, or *streichzeitige Milzruptur* of the Germans) represents about 14 per cent (1 in 7) of all splenic ruptures. This syndrome is especially insidious and treacherous because of the almost symptom-free latent period, but the delay offers an opportunity for diagnosis and treatment.

Delayed splenic rupture is most common in males in the third decade of life. Falls and traffic accidents are the most common etiologic agents. About 50 per cent of the secondary ruptures occur after an interval of less than seven days, while in an additional 25 per cent the latent period ends during the second week. Fractured ribs on the left side occur in about 10 per cent of the cases, while Kehr's sign (pain in the left shoulder due to irritation of the phrenic nerve) is present in about 28 per cent or more of cases. Other diagnostic aids include those used in diagnosing any type of splenic rupture, such as sudden collapse or shock, rapid or increasing pulse rate, progressive anemia, white cell count from 12,000 to 20,000, absence of temperature over 99 F., pain, tenderness, dullness and rigidity in the left upper quadrant, and in some instances signs of free fluid in the peritoneal cavity.

Without operation the mortality ranges from 77 to 100 per cent. At the time of McIndoe's review (1932) the operative mortality was

27 per cent, but during the past decade it has been only 10 per cent. When splenic laceration is suspected the patient should be kept in bed under close observation. In more definite cases, or at the first sign of secondary hemorrhage, splenectomy should be performed. Adequate treatment of shock with plasma or whole blood forms a necessary adjunct to the operative procedure.

ADDENDUM.—Since this paper was written a review on the subject has been published by W. H. Bucermann. In this article 2 additional cases are reported. In the first, that of a man aged 22 years, the rupture occurred thirty-eight days after he hit the left side of his chest and abdomen against a steering mechanism when his ship was torpedoed. The second is the case of a seaman aged 17 years, whose spleen ruptured four days after a fall on a dock. Addition of Bucermann's 2 cases brings the total of reported instances of delayed splenic rupture to 179.

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# INORGANIC PHOSPHORUS CONTENT OF THE SERUM IN SHOCK

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In a recent study of experimental crush injuries great elevation of creatine in the blood and the urine was observed.<sup>1</sup> This elevation was believed to arise chiefly from injury to skeletal muscle. Since at least a large part of the creatine in muscle exists in combination with phosphoric acid, it seemed likely that inorganic phosphate would also be liberated. Accordingly, the levels of serum inorganic phosphorus were determined for several animals subjected to these injuries and were found to be strikingly high. A more detailed study, including shock produced by other methods, was then undertaken.

## EXPERIMENTAL METHOD

Dogs were used in all experiments. Anesthesia was produced by the subcutaneous injection of 0.030 Gm. of morphine sulfate followed thirty minutes later by the intravenous injection of soluble pentobarbital U. S. P. (pentobarbital sodium) in doses of 0.02 Gm. per kilogram of body weight. Subsequent injections of 0.006 Gm. per kilogram were occasionally necessary. Arterial pressures were determined by direct puncture of the femoral artery. Hematocrit readings were made with Wintrobe tubes. Serum inorganic phosphorus levels were determined by the method of Fiske and Subarrow.<sup>2</sup> Immediately after withdrawal of blood samples from animals subjected to trauma by hammer blows or crush injury, an equal amount of blood from another animal was injected in order to exclude the effect of hemorrhage. Shock was produced by crush injury of an extremity, by hammer blows to an extremity and by hemorrhage.

The method and other details of the experiments on crush injury have been reported elsewhere.<sup>1</sup> For 12 of the animals subjected to these injuries, serum inorganic phosphorus levels were determined at the beginning of the experiment, at one hour, two hours, three hours, four hours, four and a half hours, five hours, five and a quarter hours, five and a half hours, six hours, seven to eight hours, and nine to eleven hours. In the experiments in which shock was produced by

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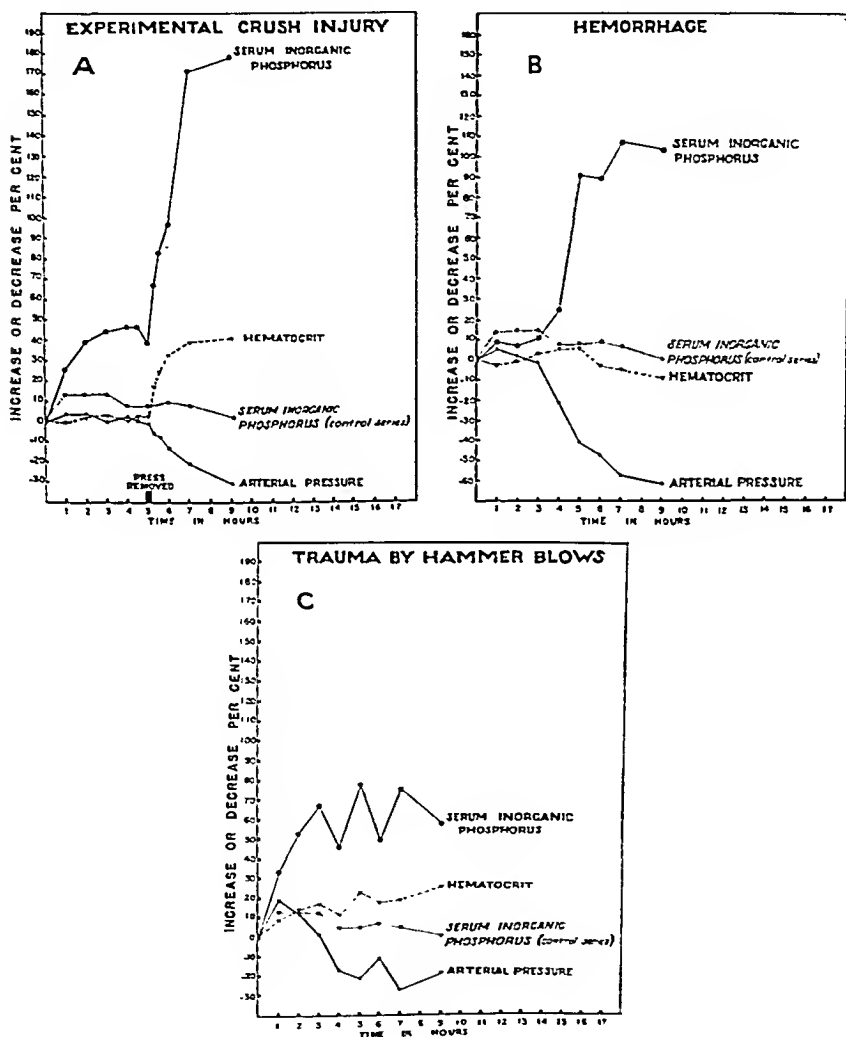
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hammer blows, repeated blows as nearly uniform as possible were administered to the soft tissues of a hindlimb, care being taken to avoid the large vessels and nerves. Shock due to hemorrhage was produced by withdrawal of blood from the femoral vein in amounts equaling 0.5 per cent of body weight at thirty minute intervals until the arterial pressure fell to approximately 70 mm. of mercury.



Changes observed in serum inorganic phosphorus, arterial pressure and hematocrit reading in shock produced by experimental crush injury, trauma by hammer blows and hemorrhage. The values expressed in percentages are computed from the averages of the experiments in each group.

In some animals subsequent bleeding was necessary to maintain the pressure at this level. In the case of hemorrhage and of trauma produced by hammer blows, serum inorganic phosphorus levels were determined hourly for the first six hours.

Subsequent observations were made at seven to eight hours and again at nine to eleven hours. In all three groups of experiments the hematocrit reading and the arterial pressure were observed at the same intervals at which the serum inorganic phosphorus level was determined.

Several control experiments were performed in order to determine the effects of anesthesia on the level of serum inorganic phosphorus. The animals were restrained on tables as in the other types of experiments and were given morphine sulfate and soluble pentobarbital (pentobarbital sodium) as already described.

### RESULTS

The results are summarized in tables 1, 2, 3 and 4 and the chart.

*Control.*—There were 8 control experiments. Elevation above the control levels of serum inorganic phosphate was observed in 6 of the 8 experiments. The elevation was greater in 1 animal than in the

TABLE 1.—*Serum Inorganic Phosphorus (Milligrams per Hundred Cubic Centimeters) as Affected by Anesthesia and Restraining Animal on Table for Several Hours (Control Series)*

Dog	Control	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	6 Hr.	7 to 9 Hr.	9 to 12 Hr.
1.....	4.0	4.2	4.7	4.6	4.2	4.3	4.5	4.3	4.3
2.....	4.6	4.8	4.1	4.3	4.4	4.6	4.6	4.6	4.6
3.....	4.2	8.3	9.1	9.9	7.1	7.1	6.9	6.6	3.1
4.....	7.3	8.3	8.3	7.7	7.1	7.0	6.8	5.8	6.8
5.....	7.4	8.3	7.6	7.3	7.0	7.1	7.7	7.1	8.1
6.....	7.9	7.2	5.8	5.2	4.4	5.0	4.4	5.9	6.2
7.....	3.6	2.7	3.0	3.6	3.6	4.3	4.6	4.5	4.0
8.....	4.1	4.9	5.9	5.9	7.6	6.2	6.8	7.0	6.5
Average Increase or decrease.....	5.4	6.1	6.1	6.1	5.7	5.7	5.8	5.7	5.5

remainder of the group. The average of the group showed a slight increase during the first three hours, after which there was a decline to approximately the initial level at nine to twelve hours.

*Crush Injury.*—There were 12 experiments in which crush injury was used. During the five hour period in which the press was on the thigh no significant change in arterial pressure was noted. No significant hemoconcentration occurred, the average for the entire group being only 1.2 per cent above the control values at the end of five hours. During the same period an increase in the level of serum inorganic phosphorus occurred, and although the increase was slight in some animals, the average rise was greater and more sustained than that observed in the group of animals subjected to anesthesia alone.

On removal of the mechanical press at the end of five hours, rapid changes in all the criteria under observation became evident. Within fifteen minutes after removal of the press the hematocrit reading showed

TABLE 2.—S<sub>erum Inorganic Phosphorus Changes (Milligrams per Hundred Cubic Centimeters) Following Experimental Crush Injury</sub>

Post	Control	1 Hr.	2 Hr.	3 Hr.	1 Hr.	4 Hr.	5 Hr.	5 Hr.	5 Hr.	6 Hr.	7 to 8 Hr.	9 to 11 Hr.	Comment
1	Serum inorganic phosphorus (mg. per 100 cc.).....	2.7	3.0	4.5	4.5	4.6	5.5	4.6	6.2	7.9	11.7	18.0	No therapy; died 12 hr. after press was removed
	Hematocrit reading.....	66.0	55.3	51.8	51.0	54.8	58.3	56.8	62.3	60.4	60.8	70.1	
	Arterial pressure (mm. of mercury)	120	120	130	130	130	130	120	120	105	85	75	
2	Serum inorganic phosphorus (mg. per 100 cc.).....	5.2	7.2	6.3	7.3	8.0	7.8	5.3	7.8	8.4	7.0	7.7	No therapy; died 9 hr. after press was removed
	Hematocrit reading.....	51.3	53.0	54.2	50.3	48.2	47.7	47.8	60.8	60.6	68.8	67.0	
	Arterial pressure (mm. of mercury)	135	135	135	135	135	130	130	110	95	75	45	
3	Serum inorganic phosphorus (mg. per 100 cc.).....	3.1	4.8	4.9	6.3	4.0	5.0	5.3	5.3	7.0	11.2	0.7	No therapy; died 9 hr. after press was removed
	Hematocrit reading.....	12.9	41.7	46.0	41.8	40.3	46.8	49.0	57.3	60.7	68.1	70.2	
	Arterial pressure (mm. of mercury)	125	135	130	125	130	130	125	120	105	110	50	
4	Serum inorganic phosphorus (mg. per 100 cc.).....	5.5	5.0	7.2	6.7	7.0	7.2	7.4	8.2	9.0	10.1	11.7	No therapy; died 12 hr. after press was removed
	Hematocrit reading.....	41.3	45.4	47.7	51.2	48.4	48.2	49.3	53.1	58.0	62.8	61.7	
	Arterial pressure (mm. of mercury)	125	125	120	130	115	115	120	115	95	90	70	
5	Serum inorganic phosphorus (mg. per 100 cc.).....	4.8	4.9	5.0	6.1	7.1	6.1	5.9	6.1	8.2	17.7	....	No therapy; died 2 hr. 15 min. after press was removed
	Hematocrit reading.....	42.2	46.2	46.8	48.3	41.8	43.0	42.3	51.3	67.7	72.7	....	
	Arterial pressure (mm. of mercury)	130	120	125	125	130	125	125	105	85	50	....	
6	Serum inorganic phosphorus (mg. per 100 cc.).....	1.1	5.4	5.4	4.5	4.8	1.8	1.8	7.5	8.5	12.5	9.0	No therapy; died 5 hr. 15 min. after press was removed
	Hematocrit reading.....	53.2	40.0	40.1	51.3	48.4	40.7	38.0	65.1	75.8	77.0	78.0	
	Arterial pressure (mm. of mercury)	130	135	130	130	135	130	130	125	100	90	60	
7	Serum inorganic phosphorus (mg. per 100 cc.).....	3.7	1.1	4.9	6.7	5.4	5.3	5.0	6.1	7.0	9.1	8.7	Pneumatic cuff applied for 18 hr.; died 25 hr. after press was removed
	Hematocrit reading.....	53.8	51.0	51.8	50.3	50.3	51.5	51.4	62.3	70.0	70.4	76.3	
	Arterial pressure (mm. of mercury)	120	130	130	130	130	130	130	125	130	115	110	
8	Serum inorganic phosphorus (mg. per 100 cc.).....	1.2	0.8	5.8	5.0	0.2	8.1	8.2	10.0	0.1	12.2	13.3	Pneumatic cuff applied for 18 hr.; died 25 hr. after press was removed
	Hematocrit reading.....	47.7	59.0	50.0	47.7	47.0	47.2	17.7	53.2	67.8	93.2	93.6	
	Arterial pressure (mm. of mercury)	130	140	140	135	130	135	135	125	130	130	130	
9	Serum inorganic phosphorus (mg. per 100 cc.).....	4.0	4.8	5.1	5.0	5.4	5.1	5.5	6.0	7.0	11.9	10.1	Pneumatic cuff applied for 18 hr.; recovered
	Hematocrit reading.....	55.2	50.7	57.7	50.1	01.0	01.4	03.0	63.9	65.1	65.1	60.7	
	Arterial pressure (mm. of mercury)	135	130	130	120	125	120	115	110	100	100	95	
10	Serum inorganic phosphorus (mg. per 100 cc.).....	3.4	4.0	7.8	5.5	7.1	5.8	5.1	7.0	8.8	11.1	9.0	Pneumatic cuff applied for 18 hr.; recovered
	Hematocrit reading.....	50.0	50.2	51.7	51.3	52.8	51.4	51.0	50.0	63.2	67.0	66.4	
	Arterial pressure (mm. of mercury)	130	135	135	130	140	140	110	130	130	125	120	
11	Serum inorganic phosphorus (mg. per 100 cc.).....	4.2	4.8	6.0	6.9	6.2	5.8	6.8	7.7	7.1	11.5	7.3	Pneumatic cuff applied for 18 hr.; recovered
	Hematocrit reading.....	63.7	63.3	15.7	11.5	13.1	11.2	10.8	40.7	55.0	58.0	60.3	
	Arterial pressure (mm. of mercury)	120	110	135	125	135	130	120	120	120	115	115	
12	Serum inorganic phosphorus (mg. per 100 cc.).....	5.7	7.4	7.7	8.1	8.1	7.8	7.8	8.0	11.9	13.5	20.8	Pneumatic cuff applied for 18 hr.; died 16 hr. after press was removed
	Hematocrit reading.....	50.2	47.3	47.7	51.4	47.4	48.0	47.0	61.0	72.2	71.8	80.1	
	Arterial pressure (mm. of mercury)	125	130	130	125	125	125	125	115	120	125	100	
Average increase or decrease													
	Serum inorganic phosphorus (mg. per 100 cc.).....	4.3	5.4	0.0	0.2	6.3	6.3	6.0	7.2	8.5	11.7	12.0	
	Hematocrit reading.....	10.4	40.2	50.3	50.2	40.6	40.8	50.2	57.8	65.6	68.7	69.4	
	Arterial pressure (mm. of mercury)	127.1	132.1	130.8	127.1	128.8	127.5	125.4	110.2	110.0	100.8	89.2	

a distinct increase and arterial pressure had begun to decline. The hematocrit reading at nine to eleven hours averaged 69.4, while the control average was 49.4. Arterial pressure had declined from the control value of 127.1 mm. of mercury to 88.2 mm. Serum inorganic phosphorus showed a sharper more progressive rise from its five hour level, averaging 12.0 mg. per hundred cubic centimeters at nine to eleven hours. This represented a rise of 179 per cent over the average control value of 4.3 mg. per hundred cubic centimeters. Six of these animals were treated by application of pressure to the injured extremity with a pneumatic cuff,<sup>1</sup> but distinct alterations in the criteria under observation occurred in spite of this form of therapy. Eight of the 12 animals died in an average time of eleven and three-tenths hours following removal of the mechanical press.

*Hemorrhage.*—There were 8 experiments in which hemorrhage was employed. The average duration of life was eight and seven-tenths hours. A decline in arterial pressure was observed in an average of four hours after bleeding was begun. The changes in hematocrit readings were not great; a slight average rise was noted four to five hours after bleeding was begun. This rise was followed by a decline in those animals which survived for longer periods. Distinct changes in serum inorganic phosphorus were observed, but in these experiments the early rise in inorganic phosphate was less pronounced than it was in the experimental crush injuries or with trauma produced by hammer blows. Elevation of inorganic phosphate was observed before the arterial pressure fell in 5 experiments, at the time of fall in arterial pressure in 1 experiment and following the fall in arterial pressure in 2 experiments. The average early values of this group more nearly conform to the early average values of the control series than do those of either of the other groups. Blood drawn at the time of death from the hearts of 3 of these animals and from the femoral vein of another showed an average of 22.5 mg. per hundred cubic centimeters.

*Trauma by Hammer Blows.*—There were 5 experiments in which trauma by hammer blows was used. Four of the 5 animals died in an average time of seven and nine-tenths hours following trauma. Progressive hemoconcentration occurred in the animals in these experiments but was not so great as in the animals subjected to crush injury. Arterial pressure declined in all experiments. Distinct elevation of serum inorganic phosphorus was observed. Two of the animals were more refractory to trauma than the others of the group; additional trauma to 1 of these at the end of six hours resulted in profound shock and death. It is to be noted that the inorganic phosphorus levels in these 2 animals

TABLE 3.—*Serum Inorganic Phosphorus (Milligrams per Hundred Cubic Centimeters) Following Hemorrhage*

Dog	Control	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	6 Hr.	7 to 8 Hr.	9 to 11 Hr.	Comment
1	Serum inorganic phosphorus (mg. per 100 cc.)	6.6	7.8	7.7	7.8	8.9	9.9	11.0	....	Died 8 hr. after hemorrhage was begun
	Hematocrit reading	55.7	50.9	52.2	55.0	56.2	52.0	52.1	....	
	Arterial pressure (mm. of mercury)	120	110	100	95	70	40	20	....	
2	Serum inorganic phosphorus (mg. per 100 cc.)	6.2	7.1	8.5	10.1	12.1	15.3	16.9	18.3	Died 10 hr. after hemorrhage was begun
	Hematocrit reading	40.3	45.5	45.5	42.2	39.8	36.4	36.6	37.6	
	Arterial pressure (mm. of mercury)	130	142	128	128	108	68	16	42	
										Died approximately 16 hr. after hemorrhage was begun
3	Serum inorganic phosphorus (mg. per 100 cc.)	5.2	6.3	4.9	5.1	7.7	9.2	8.9	7.2	
	Hematocrit reading	51.2	49.5	56.3	59.0	55.3	51.0	51.9	51.0	
	Arterial pressure (mm. of mercury)	130	132	108	86	60	65	68	68	
4	Serum inorganic phosphorus (mg. per 100 cc.)	3.8	5.2	5.1	4.2	8.8	9.8	10.1	12.2	Died 9 hr. 55 min. after hemorrhage was begun
	Hematocrit reading	41.0	38.9	39.1	45.9	48.3	13.7	11.7	11.0	
	Arterial pressure (mm. of mercury)	102	110	102	110	110	70	60	50	
5	Serum inorganic phosphorus (mg. per 100 cc.)	1.6	5.2	3.1	6.2	6.5	11.3	....	....	Died 5 hr. 50 min. after hemorrhage was begun
	Hematocrit reading	51.2	50.2	53.7	59.2	61.2	58.1	....	....	
	Arterial pressure (mm. of mercury)	124	112	110	138	131	78	....	....	
6	Serum inorganic phosphorus (mg. per 100 cc.)	7.9	8.5	7.8	7.2	9.1	20.1	....	....	Died 5 hr. after hemorrhage was begun
	Hematocrit reading	39.8	37.9	37.8	39.2	35.3	....	....	....	
	Arterial pressure (mm. of mercury)	100	104	101	110	62	....	....	....	
7	Serum inorganic phosphorus (mg. per 100 cc.)	6.7	6.9	5.7	5.1	6.3	8.2	8.0	8.6	Died 9 hr. 5 min. after hemorrhage was begun
	Hematocrit reading	45.6	43.1	43.9	41.9	41.2	44.8	45.0	43.8	
	Arterial pressure (mm. of mercury)	108	118	122	118	60	70	58	30	
8	Serum inorganic phosphorus (mg. per 100 cc.)	4.9	5.1	5.8	6.2	7.6	10.9	....	....	Died 5 hr. 40 min. after hemorrhage was begun
	Hematocrit reading	50.1	51.3	50.0	53.4	51.2	53.6	....	....	
	Arterial pressure (mm. of mercury)	116	120	126	108	16	21	....	....	
Average increase or decrease										
Average	Serum inorganic phosphorus (mg. per 100 cc.)	5.7	6.2	6.1	6.3	7.1	10.9	11.8	11.6	
	Hematocrit reading	37.6	40.1	46.2	49.1	50.3	50.3	45.5	43.1	
	Arterial pressure (mm. of mercury)	116.3	123.1	119.5	111.2	90.9	68.7	59.1	47.5	



TABLE 4.—*Serum Inorganic Phosphorus (Milligrams per Hundred Cubic Centimeters) Following Trauma by Hammer Blows to Extremity*

Dog		Control	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	6 Hr.	7 to 8 Hr.	9 to 11 Hr.	Comment
1	Serum inorganic phosphorus (mg. per 100 cc.)	5.2	12.2	15.1	18.0	....	....	....	....	....	Died 3 hr. 30 min. after trauma
	Hematocrit reading.....	41.8	47.0	49.1	50.2	....	....	....	....	....	
	Arterial pressure (mm. of mercury).....	124	136	138	93	....	....	....	....	....	
2	Serum inorganic phosphorus (mg. per 100 cc.)	4.6	6.2	6.9	7.0	7.2	6.4	5.2	6.8	8.2	Recovered
	Hematocrit reading.....	54.9	56.2	59.0	61.7	....	60.1	58.2	57.0	58.2	
	Arterial pressure (mm. of mercury).....	108	122	112	116	96	98	100	94	94	
3	Serum inorganic phosphorus (mg. per 100 cc.)	7.6	8.0	9.9	11.8	11.8	20.1	....	....	....	Died 5 hr. 10 min. after trauma
	Hematocrit reading.....	45.0	49.7	52.4	53.7	50.8	58.5	....	....	....	
	Arterial pressure (mm. of mercury).....	114	148	136	114	60	20	....	....	....	
4	Serum inorganic phosphorus (mg. per 100 cc.)	6.9	6.7	6.8	4.9	6.0	7.0	9.7	11.4	11.6	Died 14 hr. after initial trauma; additional trauma to thigh at end of 6 hr.
	Hematocrit reading.....	36.8	45.3	47.3	47.3	49.2	52.0	51.2	49.1	53.0	
	Arterial pressure (mm. of mercury).....	108	146	110	138	120	130	120	90	88	
5	Serum inorganic phosphorus (mg. per 100 cc.)	7.2	8.8	9.2	10.8	11.8	11.4	13.4	15.8	....	Died 9 hr. after trauma
	Hematocrit reading.....	43.4	42.0	43.7	44.1	42.0	46.8	47.4	52.0	....	
	Arterial pressure (mm. of mercury).....	105	110	108	102	92	94	70	58	....	
Average increase or decrease											
	Serum inorganic phosphorus (mg. per 100 cc.)	6.3	8.4	9.6	10.5	9.2	11.2	9.4	11.3	9.9	
	Hematocrit reading.....	44.4	48.0	50.5	51.8	49.3	51.3	52.3	52.7	55.6	
	Arterial pressure (mm. of mercury).....	111.8	132.5	126.8	113.4	92.0	88.0	100.0	80.7	91.0	

were not so much increased as in the animals in which shock was more profound. In the animal receiving additional trauma at the end of six hours the hyperphosphatemia increased as shock became more profound.

#### COMMENT

The breakdown of phosphocreatine following mechanical injury to skeletal muscle by hammer blows and by the mechanical press is probably responsible in part for the hyperphosphatemia observed in these experiments. Elevations of plasma creatine following muscle injury are also evidence that hydrolysis of phosphocreatine has occurred.<sup>3</sup> In the case of experimental crush injuries and possibly to a slight degree in the case of trauma by hammer blows, ischemia of the extremity is an additional factor producing breakdown of phosphocreatine. During the five hour period in which the mechanical press is on the thigh at least the major part of the blood supply to the extremity is interrupted. This ischemia and the resulting anoxia of the extremity may also cause breakdown of other organic phosphates in the tissues of the extremity with liberation of inorganic phosphate. The elevation of inorganic phosphorus was not so progressive in 2 of the animals subjected to trauma by hammer blows, although they received presumably the same amount of trauma. As shock developed after additional trauma to 1 of these animals, greater elevation of serum inorganic phosphorus was noted. This progressive increase in inorganic phosphorus as shock became more profound and the fact that marked hyperphosphatemia occurred following hemorrhage suggest that factors other than injury to muscle are contributory. The generalized anoxia and other deleterious effects of shock may be responsible for damage to tissue with breakdown of organic phosphates and liberation of inorganic phosphate.

Diminution in renal function may be partly responsible for elevation of serum inorganic phosphorus, since elevations have been shown to accompany nephritis<sup>4</sup> and cessation of renal function by ligation of the ureters.<sup>5</sup> Oliguria and elevation of blood nonprotein nitrogen have been demonstrated in cases of experimental crush injuries<sup>1</sup> and other types of trauma.<sup>3a</sup> Banaytis<sup>6</sup> reported hyperphosphatemia following trauma and emphasized its relation to disturbance of carbohydrate metabolism.

3. (a) Aub, J. C., and Wu, H.: Studies in Experimental Traumatic Shock. *Am. J. Physiol.* **54**:416, 1920. (b) Duncan and Blalock.<sup>1</sup>

4. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*. Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 1130.

5. Atchley, D. W., and Benedict, E. M.: The Distribution of Electrolytes in Dogs Following Ligation of Both Ureters, *J. Biol. Chem.* **73**:1, 1927.

6. Banaytis, S. I.: Phosphorus Content of the Blood in Traumatic Shock and in Trauma to the Central Nervous System, *Vestnik khir.* **56**:43, 1938.

Owing to the inverse relation which exists between the blood levels of phosphate and calcium ions, such elevations of phosphate will result in the withdrawal of calcium from the blood and may therefore be a factor in the production of increased permeability of the capillaries, which is believed by most investigators to occur in shock. Chambers and Zweifach<sup>7</sup> have shown that perfusion with calcium-free solutions produces an excessive leakiness of the walls of the capillaries. In view of these elevations of inorganic phosphate, determinations of ionized calcium are indicated in experiments of this type because of possible relations to capillary permeability and neural and muscular function in shock. Excessive inorganic phosphate may be one of the contributing so-called toxic factors in the irreversible shock which has been shown to result when extremities are subjected to trauma and prolonged ischemia.<sup>8</sup> Inorganic phosphate may also contribute to the renal lesions seen in clinical cases of crush syndrome, since ischemia and muscular injury of one or more extremities were present in all reported cases.

It is of interest to note that the serum inorganic phosphate levels showed some elevation in the control group of animals, subjected to anesthesia alone, and that the elevation was greater in some animals than in others. This elevation may have been related to depth of anesthesia, nutritional state and age as well as to other factors. The initial inorganic phosphate levels in all the groups appear to range rather widely. Single specimens drawn from 12 dogs under similar conditions had concentrations ranging from 3.3 to 7.9 mg. per hundred cubic centimeters, averaging 5.2 mg.

Whether or not serum inorganic phosphorus levels can be used as an index of clinical shock, either as an early sign or as a prognostic sign, will require further investigation. In the limited number of cases thus far observed the results have not been so marked as in these experiments. The greatest elevation has been noted in cases of severe muscular injury.

#### SUMMARY

The effects of shock produced by experimental crush injury, by hammer blows and by hemorrhage on the level of serum inorganic phosphorus have been studied.

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7. Chambers, R., and Zweifach, B. W.: The Structural Basis of Permeability and Other Functions of Blood Capillaries, *J. Cell. & Comp. Physiol.* **15**: 255, 1940.

8. Duncan, G. W., and Blalock, A.: Shock Produced by Crush Injury: Effects of Administration of Plasma and Local Application of Cold, *Arch. Surg.* **45**:183 (Aug.) 1942; The Effects of Application of a Tourniquet on the General Response to Gross Trauma to an Extremity, Surgery, to be published.

Serum inorganic phosphorus is elevated in shock produced by each of these methods. The time relation between this elevation of inorganic phosphate and changes in the hematocrit reading and the arterial pressure are recorded in the tables and the graphs. Hyperphosphatemia occurred early in most of the experiments in which shock was produced by experimental crush injury and by hammer blows. This early elevation was not as marked or as consistent in the experiments in which shock was produced by hemorrhage.

The possible origin of this hyperphosphatemia and its relations to some of the physiologic aspects of shock are discussed.

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# CLOT RESISTANCE IN MICE AND THE MECHANISM OF HEMOSTASIS

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During previous studies we found that movement of the tail had a slight effect or none in prolonging the duration of bleeding from a wound in the tail in normal mice. In heparinized mice, however, such movements initiated bleeding which persisted several minutes.<sup>1</sup> We also observed that some of the mice treated with heparin or dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin])<sup>2</sup> which had normal bleeding times continued to bleed spontaneously from the same wound after completion of the test. In an attempt to elucidate the lack of correlation between the bleeding time and this tendency to spontaneous bleeding from the same prick wound, further experiments were done. Macfarlane<sup>3</sup> has drawn attention to the fact that there is no satisfactory method to test the toughness of blood clots. We proposed to estimate clot resistance,<sup>4</sup> that is, the firmness of a clot and its adhesiveness, in a wound in the tail of a mouse by applying cuff pressure after bleeding had stopped. A cuff pressure of 75 mm. of mercury was applied proximal to the wound after the bleeding time test to ascertain if congestion of the tail would renew bleeding. Since heparin and dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) have anticoagulant action and sometimes prolong the bleeding time, these agents were used to study clot resistance. Our observations cast new light on the control of hemorrhage and therefore necessitate a discussion of the mechanism of hemostasis.

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1. Copley, A. L., and Lalach, J. J.: The Experimental Production of a Hemophilia-Like Condition in Heparinized Mice, *Am. J. Physiol.* **135**:547 (Feb.) 1942.

2. Lalach, J. J.; Lalach, M. H., and Copley, A. L.: Bleeding Time in Mice Following the Oral Administration of 3,3'-Methylene-bis (4-Hydroxycoumarin). Surgery, to be published.

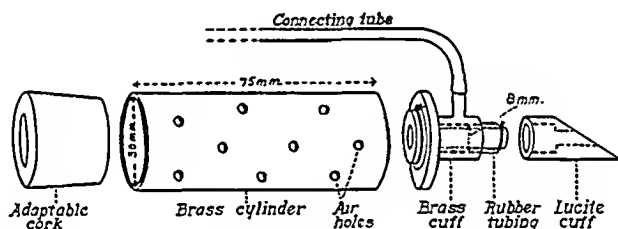
3. MacFarlane, R. G.: Critical Review: Mechanism of Haemostasis, *Quart. J. Med.* **10**:1 (Jan.) 1941.

4. Copley, A. L., and Lalach, J. J.: Bleeding Time, Lymph Time and Clot Resistance in Men, *J. Clin. Investigation* **21**:145 (March) 1942.

## METHODS

The mouse was enclosed in a brass cylinder which was suspended at an angle of approximately 40 degrees, so that the tail was immersed in a bath of physiologic solution of sodium chloride of constant temperature (37.5 C.), as previously described.<sup>1</sup> After the wound had been inflicted the duration of bleeding could easily be observed and timed as the blood emerged from the wound and escaped into the saline bath. At intervals varying from 0 to 466 minutes following the bleeding time tests the mice had cuff pressures of 75 mm. of mercury exerted at the base of the tail for one minute. This cuff pressure was arbitrarily chosen in order to standardize the test. When the cuff pressure was applied, the wound was observed for a renewal of bleeding. To exert cuff pressure on the mouse's tail, a brass cuff was constructed (figure). The cuff was 3.8 cm. long, with a central hole 8 mm. in diameter which was lined with surgical drain tubing. The cuff was connected to a mercury manometer with a rubber tube. The proximal part of the cuff fitted into the cylinder which held the mouse. A piece of lucite was fitted on the distal part of the cuff and kept the mouse's tail suspended.

Adult male and female mice fed Friskies dog food (Albers Milling Company, Seattle)<sup>4a</sup> and crushed oats were used.



Apparatus for determining clot resistance.

Three types of wounds were made on the tails of normal mice, to establish if the size of the wound would affect the bleeding time or the clot resistance. In 55 mice, 1 to 2 mm. of the tip of the tail was amputated with sharp scissors. In 98 mice, cutaneous incisions measuring 3 to 6 mm. in length and varying in depth were made on the lateral, distal portion of the tail with a razor blade. In 109 mice venous and arterial prick wounds were made in the middle portion of the tail with a pointed stylet measuring 0.5 by 1.5 mm. These 109 normal mice showed uniform results in bleeding time; hence this group served as control for subsequent experiments.

4a. Friskies Dog Food, according to the manufacturer, contains meat and bone scraps, ground wheat, soybean oil meal, ground corn, ground hulled barley, oat meal, dried skimmed milk, wheat bran, wheat germ meal 3 per cent, liver meal 3 per cent, dried beet pulp and molasses 3 per cent, fish meal 3 per cent, steamed bone meal 2 per cent, dextrin 3 per cent, charcoal 0.25 per cent, sardine oil (100 A. O. A. C. chick units of vitamin D per gram; 3,000 U. S. P. units of vitamin A per gram) 0.15 per cent, salt 0.25 per cent, iron oxide 0.125 per cent and irradiated brewers' type yeast 0.05 per cent. The guaranteed chemical analysis is as follows: protein (minimum) 22 per cent, fat (minimum) 3.5 per cent, fiber (maximum) 4 per cent, nitrogen-free extract (minimum) 45 per cent, ash (maximum) 10 per cent and moisture (maximum) 10 per cent.

One part of dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin])<sup>5</sup> was dissolved in 1,000 parts of a 0.1 per cent solution of sodium carbonate and administered orally with a blunt 18 gage needle. The mice received daily doses of 30 to 60 mg. per kilogram of body weight for three days, and the tests were done on the fourth day. Heparin (Connaught Laboratories, University of Toronto, 110 Murray-Best units per milligram) was injected subcutaneously from 239 to 403 minutes before the tests were done. The mice received 50, 100, 200 and 400 units per 20 Gm. of body weight. Clot resistance was measured by application of a cuff pressure of 75 mm. of mercury or by observation of spontaneous bleeding. Spontaneous bleeding was manifest either when the animal was left undisturbed in the cage or as the mouse was placed in the brass cylinder for the clot resistance test. All mice

TABLE 1.—*Duration of Bleeding from Different Parts of the Tail and the Effect of Cuff Pressure on the Clot Resistance in Normal Mice*

Amputation of Tail				Cutaneous Incision 3 to 6 Mm. in Length			
Mouse Number	Duration of Bleeding, Seconds	Interval Between Bleeding and Clot Resistance Test, Min.	Effect of 75 Mm. Hg Cuff Pressure for 1 Minute	Mouse Number	Duration of Bleeding, Seconds	Interval Between Bleeding and Clot Resistance Test, Min.	Effect of 75 Mm. Hg Cuff Pressure for 1 Minute
58	189	0	—	24	30	21	—
57	44	0	—	2	91	30	—
54	7	0	+	3	137	32	+
51	56	0	+	39	58	37	—
52	30	0	+	47	85	37	+
95	43	0	+	26	88	38	+
53	45	16	+	44	51	41	+
4	..	18	—	48	186	45	+
43	41	21	—	33	430	47	+
1	..	24	—	25	97	49	—
19	..	24	+	35	62	50	—
10	..	29	—	37	76	53	—
5	..	30	—	80	102	53	—
8	..	38	+	40	98	56	—
11	..	38	—	42	174	59	—
2	..	40	+	34	205	63	+
59	665	42	—	31	53	72	+
6	...	45	—	43	288	76	—
9	...	52	+	45	105	130	+
56	704	..	..	49	669	152	+

+, bleeding; —, no bleeding.

were examined for spontaneous bleeding two or three times per hour during the first four hours following the bleeding time test. The term "bleeding time" is restricted to the value shown by the initial bleeding time test and does not include recurrent bleeding due to decreased clot resistance.

#### RESULTS

Table 1 shows the effect of amputation wounds and cutaneous incision wounds on the duration of blood flow and the renewal of bleeding after application of cuff pressure. Twenty mice out of each group are presented in the table.

5. Supplied by Dr. J. F. Biehn, Abbott Laboratories, North Chicago, Ill.

Bleeding times from amputation wounds varied from 7 to 704 seconds in 11 mice. A cuff pressure of 75 mm. of mercury for 1 minute provoked bleeding in 22 of the 55 mice studied. Nine mice had the cuff pressure applied after 11 to 54 minutes with a renewal of blood flow. In 7 mice pressure initiated bleeding after 0 to 24 minutes but failed on the second trial 18 to 44 minutes later. After being handled 8 to 27 minutes following amputation 4 mice bled spontaneously, but they did not show renewal of blood flow when cuff pressure was applied 23 to 84 minutes after the first handling. One mouse did not bleed when pressure was applied immediately, but bled spontaneously in the cage 28 minutes later. One mouse was tested twice, immediately and 28 minutes later, with a renewal of bleeding on both occasions. It is not possible to amputate the tip of the tail without cutting veins or the artery in some mice. Some amputation wounds had a diameter up to three times that of others, because of anatomic variations in the tip of the tail. The blood oozed from the wound when only the capillaries were cut. When larger vessels were severed the blood loss was greater and the duration of bleeding was longer.

Bleeding time from cutaneous incision wounds in 28 mice varied from 21 to 669 seconds. In 85 mice cuff pressure was applied once. Twenty-four mice out of this group showed renewed bleeding after 32 to 466 minutes, while 61 mice failed to exhibit bleeding during a similar time. Repeated clot resistance tests were done on 4 other mice. Two of them bled spontaneously after handling at 52 and 68 minutes. Cuff pressure initiated bleeding on three occasions in 1 mouse at 45, 120 and 375 minutes. The fourth mouse bled when pressure was applied at 152 and 413 minutes. The larger wounds showed an increased tendency to renewed bleeding on application of cuff pressure.

In the third group of mice a vein of the tail was cut across its long axis, about 5 cm. from the base of the tail. The bleeding times of 109 mice agreed with previous venous bleeding times.<sup>6</sup> Not a single mouse in this group bled spontaneously in the cage or after handling. However, after application of cuff pressure after 18 to 34 minutes renewed bleeding occurred only in 6 mice, which were excluded from further studies. The remaining 103 mice were treated either with dicoumarin or with heparin and studied subsequently.

#### EXPERIMENTS WITH DICOUMARIN

Three series of 10 mice received dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) in doses of 30, 50, and 60 mg. per kilogram of body weight. To one series of 30 mice 40 mg. per kilogram was administered. During the period of treatment 5 of the mice receiving 60 mg.

6. Footnotes 1 and 2.



per kilogram died; whereas only 1 mouse among those receiving 40 and 50 mg. per kilogram died. Results on 12 mice with decreased clot resistance are compiled in table 2.

TABLE 2.—*Bleeding Time and Clot Resistance in Mice Before and After Oral Administration of Dicoumarin (3,3'-Methylene-bis-[4-Hydroxycoumarin]) for Three Days*

Number	Control			After Treatment with Dicoumarin			
	Bleeding Time, Seconds	Interval Between Bleeding Time and Clot Resistance, Minutes	Clot Resistance Against 75 Mm. Hg Cuff Pressure for 1 Minute	Mg./Kg. Daily	Bleeding Time, Seconds	Interval Between Bleeding Time and Clot Resistance, Minutes	Clot Resistance Against 75 Mm. Hg Cuff Pressure for 1 Minute
1	57	78	—	30	54	37 109	+* —
2	33	15	—	30	900	19 78 128 171 244	+* +* +* +* +*
3	71	20	—	40	40	19 87	+ —
4	102	13	—	40	30	19 58 139 240	+ + + —*
5	29	18	—	40	75	20 83	+ —
6	24	19	—	40	61	21 48	+ —
7	58	16	—	40	25	22 134 182 260	— +† +* —*
8	31	13	—	40	80	32 90 250	+ + —
9	40	14	—	50	900	13 72	+* —
10	54	16	—	50	123	17 31 119	+* +* —
11	34	13	—	60	30	28 103	+* —
12	38	20	—	60	100	24 63 180	+* + +†

+, bleeding; —, no bleeding.

\* Without cuff pressure during handling.

† In the cage.

Three of the 10 mice treated with 30 mg. per kilogram exhibited bleeding during handling. One mouse had a normal bleeding time and spontaneous bleeding after 37 minutes; however, pressure after 109 minutes did not provoke a blood flow. The second mouse also had a normal bleeding time with spontaneous bleeding at 19, 77, 115, 165 and 282

minutes. The third mouse had a bleeding time longer than 15 minutes, and spontaneous bleeding occurred at 19, 78, 128, 171 and 244 minutes. A fourth mouse in this group had a bleeding time longer than 15 minutes and died before the clot resistance test could be done. The remaining 6 mice had normal bleeding times, and cuff pressure did not initiate bleeding.

Nine of the 30 mice treated with 40 mg. per kilogram had a decreased clot resistance, and 29 mice had normal bleeding times. One mouse had a bleeding time longer than 15 minutes and showed spontaneous bleeding during handling at 29 minutes. In 3 of the 9 mice cuff pressure renewed bleeding two and three times within 139 minutes. A fifth mouse had a normal clot resistance after 22 minutes but began to bleed spontaneously in the cage after 134 minutes and after 182 minutes during handling. Cuff pressure provoked bleeding in the remaining 4 mice after 19 to 32 minutes but failed to do so after 48 to 250 minutes.

Four of the 9 mice treated with 50 mg. per kilogram had a decreased clot resistance. This was observed mostly during handling of the mice. One mouse with a bleeding time longer than 15 minutes had spontaneous bleeding after 13 minutes during handling, but pressure failed to induce bleeding after 72 minutes. The second mouse had a normal bleeding time and showed spontaneous bleeding in the cage at 11, and during handling at 75 and 114 minutes. Two other mice with normal bleeding times bled spontaneously at 17, 31 and 29 minutes during handling but failed to bleed when pressure was applied after 119 and 98 minutes respectively. A fifth mouse had a bleeding time of nine minutes and died during the test. The 4 remaining mice had normal values.

Three of the 5 mice treated with 60 mg. per kilogram had a decreased clot resistance during handling. One mouse with a normal bleeding time bled spontaneously for 20 minutes in the cage and at 28 minutes during handling, but after 103 minutes pressure did not provoke bleeding. A second mouse had a normal bleeding time, bled spontaneously during handling at 24 minutes, required pressure to initiate bleeding at 63 minutes, bled in the cage after 3 hours and subsequently died of hemorrhage. The third mouse had a normal bleeding time, and pressure initiated bleeding at 20 minutes. The fourth mouse had a bleeding time longer than 15 minutes and died. The fifth mouse had a normal bleeding time and a normal clot resistance.

#### EXPERIMENTS WITH HEPARIN

Heparin was injected into four groups of 43 mice. Four mice received 400 units; 4 were given 100 units, and 3 had 50 units. Thirty-two mice received 200 units; the results on 15 of these mice are listed in table 3.

Seven mice which received 50 and 100 units of heparin exhibited normal bleeding time and clot resistance. Three of the 36 mice which were treated with 200 and 400 units died before studies were done.

TABLE 3.—*Comparison Between Bleeding Time and Clot Resistance in Mice Before and After Subcutaneous Injection of Two Hundred Units of Heparin per Twenty Grams of Weight*

Number	Before Injection			After Injection			
	Bleeding Time, Seconds	Interval Between Bleeding Time and Clot Resistance, Minutes	Clot Resistance Against 75 Mm. Hg Cuff Pressure for 1 Minute	Duration of Action of Heparin Until Bleeding Time Test, Minutes	Bleeding Time, Seconds	Interval Between Bleeding Time and Clot Resistance, Minutes	Clot Resistance Against 75 Mm. Hg Cuff Pressure for 1 Minute
1	90	25	—	301	35	10 84	— +
2	38	23	—	389	230	17 46	— +
3	59	31	—	369	900	18 97	+† +
4	55	34	—	342	57	19 131	— —
5	80	22	—	247	67	20 125	— +
6	117	29	—	328	780	20 139	— +
7	61	31	—	239	190	20 149	— +
8	62	12	—	350	24	22 118	— —
9	25	33	—	307	85	22 75 160	— +† +
10	70	23	—	263	250	28 120 238	+* + +
11	67	29	—	322	45	31 145	— —
12	70	29	—	323	45	31 143	— +
13	60	20	—	393	30	32 91	— +*
14	52	20	—	401	900	33 65	— +*
15	38	23	—	403	84	47 72	— +

+, bleeding; —, no bleeding.

\* During handling.

† In the cage.

Twenty-six of the remaining 33 mice had a decreased clot resistance. Of these 26 mice, 4 had bleeding times longer than 15 minutes. In a fifth the bleeding time was 13 minutes, and in a sixth, 6 minutes. Clot resistance in 14 mice was normal when pressure was applied after 6 to 33 minutes, but bleeding was renewed when pressure was applied the

second time after 29 to 199 minutes. In 7 other mice, which did not bleed when pressure was applied the first time after 11 to 48 minutes, spontaneous bleeding developed during handling or in the cage during the second hour. Five more mice initially showed spontaneous bleeding during handling after 16 to 34 minutes and continued to bleed in the cage. After hemostasis occurred, subsequent bleeding in 3 of these mice was initiated by pressure after 124 to 126 minutes. The fourth mouse continued to bleed only during handling, while the fifth continued to bleed in the cage.

On macroscopic examination it was possible to observe that the punctured vein was either narrowed in diameter or apparently empty of blood in the region of the cut. When cuff pressure was applied the first time, the tail became congested without apparent widening in diameter of the injured part of the vein. Subsequently, after 30 to 120 minutes, this area dilated either without pressure or after cuff pressure was applied.

#### COMMENT

Whether or not a tendency to bleeding exists in an organism might be indicated by a prolonged bleeding time whenever it occurs. However, the bleeding time test is not sufficiently sensitive in most cases to indicate that a tendency to bleeding is present.<sup>7</sup> We believe that studies of clot resistance should be done in conjunction with the bleeding time test the better to demonstrate a tendency to bleeding. We have shown that probably the firmness of the clot and its property of adhesion to the traumatized vessels are important in maintaining hemostasis.<sup>4</sup> In this study we were concerned with the size of the wound and the role played by time in the formation of the clot in their relationship to clot resistance.

*The Wound Thrombus.*—We have already expressed the belief that both the agglutination of platelets and the conversion of fibrinogen to fibrin are responsible for the properties of the clot which seals the wounded vessels.<sup>4</sup> We also believe that the clot which forms in a wound is similar to or identical with a thrombus; therefore we designate such a clot as a "wound thrombus." It is still a matter of controversy whether thrombi in general can develop without injury to the endothelium<sup>8</sup>; however, in our studies of bleeding such injury is obvious. The original investigations on experimental thrombosis following traumatization of

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7. Copley, A. L., and Lalich, J. J.: The Influence of Blood Transfusion and Injectons of Bursa Pastoris (Shepherd's Purse) Extract on the Clot Resistance in Two Hemophiliacs, *Am. J. M. Sc.* **204**:665 (Nov.) 1942.

8. Silberberg, M.: The Causes and Mechanism of Thrombosis, *Physiol. Rev.* **18**:197 (April) 1938.

vessels by Eberth and Schimmelbusch<sup>9</sup> were confirmed by Welch<sup>10</sup> and further developed by Aschoff.<sup>11</sup> Eberth and Schimmelbusch observed that agglutination of platelets occurred first at the site of injury and that this was followed by coagulation of blood. Aschoff showed that retardation and not stagnation of circulating blood brings about formation of white thrombi. He suggested that the agglutination of platelets creates a condition which fosters formation of fibrin. The formation of a thrombus explains the results of our numerous observations on human beings and on mice with cutaneous wounds bleeding into physiologic solution of sodium chloride. The volume output of blood from a wound during bleeding gradually diminishes until hemostasis occurs.<sup>12</sup> This phenomenon is in sharp contrast to coagulation of whole mammalian blood in test tubes, where the clot does not form for a variable interval of time and then the blood coagulates rather suddenly. Therefore, formation of a clot during and after bleeding, we believe, is similar to the formation of a thrombus, which according to Aschoff initially is a white thrombus and with further growth becomes a mixed thrombus. We have differentiated between the firmness of the clot and its adhesiveness to the wound in the vessel.<sup>4</sup> We believe that the adhesiveness is associated with the agglutination of platelets. Eberth and Schimmelbusch suggested that the platelets undergo a viscous metamorphosis and adhere not only to each other but to the vessel wall. At present we cannot offer an explanation for the causes of firmness of a clot. However, we feel that it is mainly dependent upon the formation of the fibrin network and its properties and subsequent changes.<sup>13</sup>

*The Wound.*—We have previously suggested that variations in bleeding time may be due to differences in the size of the wound.<sup>12</sup> Although we were unable to control the size or the number of vessels cut, we endeavored to study this variable by inflicting different types of wounds, such as prick, incision and amputation wounds. There was a tendency to prolonged bleeding in amputation wounds and in incision wounds longer than 3 mm. Further, we were able to differentiate the type of vessels injured by observing the flow of blood.<sup>12</sup> The cutting of capillaries alone was indicated by the oozing of blood. The puncture of a vein or venule was manifested by the dark color

9. Eberth, J. C., and Schimmelbusch, C.: *Die Thrombose nach Versuchen und Leichenbefunden*, Stuttgart, Ferdinand Enke, 1888; cited by Welch.<sup>10</sup>

10. Welch, W. H.: *Thrombosis*, in Allbutt, T. C., and Rolleston, H. D.: *System of Medicine*, London, Macmillan & Co., 1909, vol. 6, p. 691.

11. Aschoff, L.: *Lectures on Pathology*, New York, Paul B. Hoeber, 1924, p. 253.

12. Copley and Lalich (footnotes 1 and 4).

13. Lalich, J. J., and Copley, A. L.: *A Study of Clot Firmness in Viscometer Tubes*, *Proc. Soc. Exper. Biol. & Med.*, to be published.

and the larger volume output of blood. A severed artery or arteriole, on the other hand, exhibited a pulsating flow of light red blood. In the mechanism of hemostasis all types of vessels usually are involved and should be considered. Cutaneous elasticity may affect hemostasis in different ways. It is apparent that in incision wounds smaller than 3 mm. in length or in puncture wounds, the inherent elastic property of the skin can close the margins of the wound and thus exert a resistance to bleeding. In larger wounds the elasticity of the skin can produce the opposite effect, a gaping of the margins so that they offer no resistance to bleeding. In amputation wounds of the mouse's tail the factor of cutaneous elasticity apparently does not enter into consideration. In addition to the physical factors of the skin we have postulated a humoral skin factor<sup>1</sup> which promotes the formation of a wound thrombus.

*The Influence of Cuff Pressure on the Wound Thrombus.*—After injury, formation of a thrombus<sup>9</sup> and narrowing of the lumen of the vessel<sup>3</sup> bring about hemostasis. Narrowing of the capillary lumen has been repeatedly observed to be due to endothelial swelling.<sup>14</sup> After hemostasis is established the wound thrombus may continue to deposit fibrin and corpuscular elements. The time factor, therefore, becomes important in the subsequent maintenance of hemostasis, since a wound thrombus, like an ordinary thrombus,<sup>15</sup> requires time to develop fully. With widening of the lumen the force of circulation is exerted against the wound thrombus. If the wound thrombus seals a capillary or a vein this force is negligible, but when an artery is severed the systolic pressure exerts a considerable force on the thrombus. Under normal conditions the thrombus becomes sufficiently resistant in one to two hours to withstand the pressure in small arteries. By applying cuff pressure, therefore, one simulates conditions in veins and capillaries which exist normally when wound thrombi are formed in arteries. Lewis<sup>16</sup> demonstrated that pressures up to 70 mm. of mercury are reached in the veins of human subjects within 40 seconds after cuff pressure of 70 mm. of mercury is applied to the arm. Theoretically, then, the pressure attained in the veins and capillaries will be similar to the cuff pressure when the cuff pressure does not exceed the systolic pressure minus the pressure required to maintain a flow of blood. The pressure sufficient to maintain blood flow may vary<sup>17</sup> and was found to be approximately

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14. Sanders, A. G.; Ebert, R. H., and Florey, H. W.: Mechanism of Capillary Contraction, *Quart. J. Exper. Physiol.* **30**:281 (Sept.) 1940.

15. Welch.<sup>10</sup> Aschoff.<sup>11</sup>

16. Lewis, T.: *The Blood Vessels of the Human Skin and Their Responses*. London, Shaw & Sons, 1927.

17. Copley, A. L.; Krcma, L. C., and Whitney, M. E.: Humoral Rheology: I. Viscosity Studies and Anomalous Flow Properties of Human Blood Systems with Heparin and Other Anticoagulants, *J. Gen. Physiol.* **26**:49 (Sept.) 1942.

20 mm. of mercury in dogs.<sup>18</sup> In case a higher cuff pressure is applied, a greater force is exerted on the wound thrombus. In this respect the clot resistance test is dependent on the systolic pressure. Mice have limited blood volume, and therefore loss of blood rapidly affects their systolic pressure. This was apparent in several of the mice which either stopped bleeding when the pressure was increased from 75 to 100 mm. of mercury or started to bleed when cuff pressure was reduced from 100 to 75 mm. of mercury. We found that when cuff pressure was applied during the first hour the likelihood of provoking bleeding in normal mice was greater than when the cuff pressure was applied during the next hour. There were a few mice, however, in which the time interval did not help to increase the resistance of the wound thrombus.

*Normal Mice.*—Our results show that amputation or incision wounds were of such dimensions that hemostasis was maintained with difficulty in some of the normal mice. In many of the mice the time of bleeding from these wounds was prolonged. Spontaneous bleeding occurred either while the mice were resting in their cages or as they were being placed in the brass cylinder. Another group began to bleed when cuff pressure was applied, indicating that in normal mice, when the wound exceeded a certain size, a wound thrombus, even during the first hour of its formation, was incapable of withstanding the added stress of cuff pressure. These findings show that even though larger wounds exhibited an increased tendency to renewed bleeding, a few of the mice with small wounds also bled repeatedly on application of pressure. Likewise, in spite of the time interval between the cessation of bleeding and the application of cuff pressure, which favored a normal clot resistance, some mice bled when the pressure was applied after 5 hours. These apparently contradictory results suggest that other factors besides the size and shape of the wound or the time elapsing between the tests, function in maintaining hemostasis. When puncture wounds were produced in veins or arteries the observed physical features of the wound were sufficiently uniform so that hemostasis was maintained. In puncture wounds the bleeding time was as previously reported,<sup>1</sup> and spontaneous bleeding never occurred in the 109 mice studied. Even though hemostasis was maintained under normal conditions, it was observed that the added strain of a cuff pressure of 75 mm. of mercury during the first 30 minutes following bleeding dislodged the wound thrombus and caused a renewal of bleeding in 6 of the 109 mice. These studies emphasize that experiments must be controlled before certain substances can be tested for their effect on hemostasis.

*Mice Treated with Dicoumarin.*—Treatment with dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) prolonged the bleeding time in

18. Dow, P., and Hamilton, W. F.: Analysis of Emptying of Segments of Arterial Reservoir, *Am. J. Physiol.* **127**:785 (Nov.) 1939.

some mice. Thus earlier observations were verified.<sup>2</sup> The clot resistance was found to be decreased in approximately 30 per cent of the mice. Spontaneous bleeding, which was never observed in the control series, occurred in many of the treated mice, either during handling or while the mice were in the cage. The mice bled when the cuff pressure was applied initially within 40 minutes and again during the first 2 hours following the renewed bleeding. Subsequent cuff pressure usually failed to renew bleeding. The observed increase in clot resistance after the second hour indicates that the time interval favors an increase in the firmness of the clot. This hypothesis was substantiated by an exploratory study after administration of dicoumarin to a patient with recurrent thrombophlebitis whose clot firmness, as determined by a test previously described,<sup>13</sup> was initially decreased. With time, however, it gradually increased above the firmness observed in clots from normal persons. From the normal result of a clot resistance test made 5 minutes after bleeding time in this patient had been found to be normal, it may be inferred that the adhesiveness of the wound thrombus was not impaired, although initially there was a pronounced decrease in the firmness of the clot. Nevertheless, the hemorrhagic condition induced by dicoumarin may not be solely based on prolonged coagulation and prothrombin times, or on a decreased firmness of the clot, since Bingham, Meyer and Pohle<sup>19</sup> found marked capillary dilatation in their dogs treated with dicoumarin. This phenomenon of widening of the vessel may furthermore contribute to the initially decreased clot resistance in the mice treated with this compound.

*Mice Treated with Heparin.*—Unlike the mice treated with dicoumarin, the majority of the mice given heparin did not bleed during the first 30 minutes after the bleeding time test, but after this period of time either spontaneous bleeding developed or cuff pressure provoked bleeding. It was found that more heparin is needed to prevent agglutination of platelets than to inhibit formation of fibrin.<sup>20</sup> It was suggested that heparin affects the platelets by acting with an unidentified substance in plasma which may be present in different concentrations in different bloods.<sup>21</sup> We believe, as do Best, Cowan and MacLean,<sup>22</sup>

19. Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on Hemorrhagic Agent 3,3'-Methylene-bis-(4-Hydroxycoumarin): Its Effect on Prothrombin and Coagulation Time of Blood of Dogs and Humans, *Am. J. M. Sc.* **202**:563 (Oct.) 1941.

20. Solandt, D. Y., and Best, C. H.: Time Relations of Heparin Action on Blood-Clotting and Platelet Agglutination, *Lancet* **1**:1042 (June 8) 1940.

21. Copley, A. L., and Robb, T. P.: Studies on Platelets: II. The Effect of Heparin on the Platelet Count in Vitro, *Am. J. Clin. Path.* **12**:416 (Aug.) 1942.

22. Best, C. H.; Cowan, C., and MacLean, D. L.: Heparin and Formation of White Thrombi, *J. Physiol.* **92**:20 (Feb.) 1938.



that the agglutination of platelets is due to the presence of an "adhesive agent" and not to formed fibrin. This is also evident in white thrombus formation, in which several workers were unable to demonstrate precipitation of fibrin.<sup>23</sup> In spite of injection of heparin Murray, Jaques, Perrett and Best<sup>24</sup> found that in some of their dogs thrombosis developed after injury to the blood vessel. This is also in accordance with our observations on formation of wound thrombi in mice which received excessive doses of heparin. In mice that have been given heparin growth of a thrombus will be primarily due to deposition of platelets and not to formation of fibrin. One may therefore assume that agglutination of platelets will be fostered by the skin or tissue factor<sup>1</sup> released by the injury. It may be postulated that as long as the platelets are not hyalinized<sup>22</sup> and sufficient fibrin is not deposited to form a complete mixed thrombus, heparin may act in two ways on the white thrombus. Further growth of the thrombus will be inhibited and heparin may react with the adhesive agent and thus allow disintegration of the white thrombus. We found that a time factor was necessary to allow renewed bleeding. We suggest that this is necessary so that the heparin may react with the adhesive agent. The force which is then applied by the cuff pressure dislodges the wound thrombus from its attachments to the margins of the wound.

The phenomena of bleeding time and platelet count are not generally interdependent, as MacFarlane<sup>3</sup> pointed out. These findings correspond with those of Copley and Robb,<sup>25</sup> who demonstrated that no correlation exists between bleeding time and platelet count in mice following single or repeated injections of heparin.

We have previously shown that heparin may exhaust the skin factor and that for this reason the bleeding time becomes prolonged in mice into which large amounts of heparin are injected.<sup>1</sup> In these animals the injured area has no more skin factor available and is therefore unable to form a white thrombus. The recurrence in heparin-treated mice of bleeding initiated with cuff pressure, or spontaneously, from several minutes to several hours afterward, responds, as we believe, to the same mechanism. Since the decreased clot resistance occurs in hemophilia,<sup>26</sup> it may be regarded as another feature in the produced hemophilia-like

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23. Apitz, K.: Ueber den Bau jüngster Blutplättchenthromben und den Einfluss des Novirudins auf ihre Entstehung, *Centralbl. f. allg. Path. u. path. Anat.* 50:9 (Nov. 10) 1930.

24. Murray, D. W. G.; Jaques, L. B.; Perrett, T. S., and Best, C. H.: Heparin and Thrombosis of Veins Following Injury, *Surgery* 2:163 (Aug.) 1937.

25. Copley, A. L., and Robb, T. P.: Studies on Platelets: III. The Effect of Heparin in Vivo on the Platelet Count in Mice and Dogs, *Am. J. Clin. Path.* 12:563 (Nov.) 1942.

26. Copley and Lalich (footnotes 4 and 7).

condition in heparinized mice. It has been shown that the fibrinogen is progressively but slowly converted into fibrin in both the hemophilic blood and the heparinized blood.<sup>27</sup> In this connection it is of interest that the clot firmness test<sup>13</sup> with blood clots of hemophiliacs and blood clots from rabbits treated with heparin showed the firmness to be greatly decreased. The decrease in clot firmness of blood from the heparinized animals persisted for a long time. These findings indicate not only that the attachment of a wound thrombus may become abnormal but that the firmness of the clot itself is impaired both in persons with hemophilia and in animals that have been given heparin.

#### SUMMARY

An apparatus was devised for studies of clot resistance in wounds of the tails of mice. The effect of incision, amputation and puncture wounds on the bleeding time and clot resistance in normal mice was studied. The clot resistance test was standardized in mice.

Following subcutaneous injections of large doses of heparin the clot resistance in most mice was found to be decreased. Only a portion of the mice treated with dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) exhibited decreased clot resistance. The clot which is formed in the wound is differentiated from a blood clot formed in vitro and is defined as a "wound thrombus." The probable mechanisms by which heparin and dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]) induced a hemorrhagic tendency in mice and decreased the clot resistance and also the factors involved in hemostasis are discussed.

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27. Copley, A. L.: The Phenomenon of Thixotropy in Hemophilic and Heparinized Blood, *Science* **94**:543 (Dec. 5) 1941.

## SURGICAL ANATOMY OF THE EXTERNAL CAROTID PLEXUS

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Both neurologists and surgeons have given steadily increasing consideration to the pain which accompanies vascular disease. Among the varieties is atypical facial neuralgia, in which the pain is felt in the areas supplied by the external carotid artery. Section of the sensory root of the trigeminal nerve has usually failed to relieve such pain. Other attempts to relieve it have included resection of the cervicothoracic sympathetic chain at various levels and periarterial stripping of the common carotid artery near its bifurcation. It is generally believed that the autonomic nervous system is involved in the production of atypical facial neuralgia, and on this basis attempts have been made to relieve it by severing (either preganglionically or postganglionically) the motor outflow reaching the affected sites.

After the operative treatment of atypical facial neuralgia, results are not predictable, and in some cases no relief at all is obtained. Furthermore, a Horner's syndrome results from cutting the cervical sympathetic chain. Since section of the autonomic nerves accompanying the facial artery has relieved buccal neuralgia,<sup>1</sup> it was felt that the pain in other areas might be relieved by denervating the external carotid artery without disturbing the cervical portion of the sympathetic trunk. However, the descriptions given of the branches of the superior cervical ganglion which pass to the external carotid artery are inconsistent, and data obtained from other vertebrates have often been assumed to be true of man without attempts at substantiation. This paper discusses the anatomy of the external carotid plexus plus other features of the cervical sympathetic chain.

No attempt is made here to review the literature other than that pertinent to the present problem. Siwe<sup>2</sup> thoroughly dissected the con-

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From the Department of Anatomy, Stanford University School of Medicine. This work, begun at Stanford University, was completed in the Department of Anatomy, Washington University School of Medicine, St. Louis. Dr. Frederick L. Reichert suggested the problem and made available a grant from the Kinney Neurological Research Fund, Stanford University School of Medicine.

1. Reichert, F. L.: Buccal Neuralgia: A Form of Atypical Facial Neuralgia of Sympathetic Origin, *Arch. Surg.* **41**:473-486 (Aug.) 1940.

2. Siwe, S.: The Cervical Part of the Ganglionated Cord, with Special Reference to Its Connections with the Spinal Nerves and Certain Cerebral Nerves, *Am. J. Anat.* **48**:479-497, 1931.

nections of the cervical portion of the sympathetic trunk in human beings. He emphasized that a multitude of anastomoses occur between the glossopharyngeal and the hypoglossal nerve and between the vagal and the sympathetic trunk. Connections of the vagus nerve with the first two cervical nerves were found to be constant. He also pointed out that the connections of the superior cervical sympathetic ganglion and the jugular ganglion of the vagus nerve may lead to a fusion of the two. Sheehan, Mulholland and Shafiroff<sup>3</sup> described many of the same connections in their observations on the anatomy of the carotid sinus nerve.

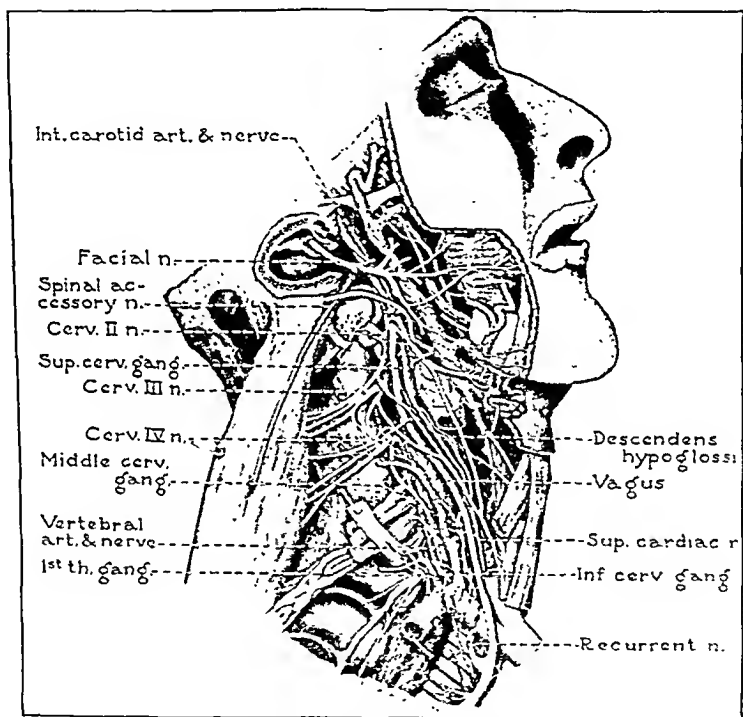


Fig. 1.—Drawing of a dissection of the right side of the head and neck. Most of the common carotid artery has been removed, and the mandible has been cut away to show the external carotid plexus. A branch entering into this plexus can be seen hooking around the hyoid branch of the superior thyroid artery. A branch of the facial nerve is seen crossing the external maxillary artery and its accompanying nerves.

#### MATERIALS AND METHODS

Twenty dissections were made in cadavers, and certain features were checked in student dissections at the Washington University School of Medicine, St. Louis. By the use of a fine sharp probe, small scissors and forceps, small nerve filaments could be traced for considerable distances in the connective tissue around the

3. Sheehan, D.; Mulholland, J. H., and Shafiroff, B.: Surgical Anatomy of the Carotid Sinus Nerve. *Anat. Rec.* 80:431-442, 1941.

blood vessels. Where differentiation from connective tissue was needed, injection of solution of sodium chloride into the larger trunks was frequently helpful. Figures 1 and 2 are drawings of a dissection of a head and a neck which showed most of the features described in this paper.

#### OBSERVATIONS

The external carotid plexus is formed in a more or less constant manner. From the superior pole of the superior cervical ganglion either one branch may arise which almost immediately splits into several or

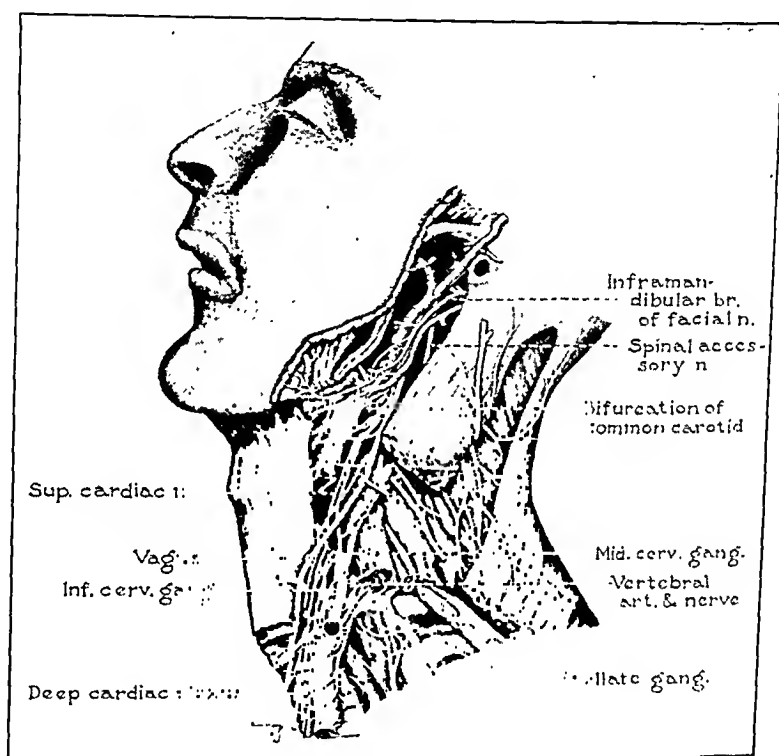


Fig. 2.—Drawing of a dissection of the left side of the head and the neck, showing the external carotid plexus with a component branch ascending from the superior thyroid artery. The deep cardiac plexus is shown encircling the left subclavian artery. A stellate ganglion is present, and lying medially is a small ganglion detached from the stellate ganglion, probably representing part of the inferior cervical ganglion.

there may be an anastomosing plexus made up of small fascicles from which three or four branches arise. One of these branches forms the twigs which enter into the formation of the intercarotid plexus described by Sheehan, Mulholland and Shafiroff. Another branch runs directly to the external carotid artery, usually to its medial side, and enters into the formation of the external carotid plexus. A third branch descends.

posterior and medial to the origin of the external carotid artery, to the superior thyroid artery. It usually anastomoses with the superior laryngeal branch of the vagus nerve and supplies the superior thyroid artery with fine filaments. Then, after passing inferior to that artery or to its hyoid branch, the nerve makes a sharp turn superiorly to ascend along the anterior surface of the external carotid artery. It supplies a few small twigs to the lingual artery, and almost immediately thereafter it anastomoses with the aforementioned branch of the superior cervical ganglion. Both branches break up into a plexus which lies in the connective tissue encircling the artery. The component branches vary in size. Filaments may be traced inferiorly to the intercarotid plexus. The occipital and ascending pharyngeal arteries are accompanied by small branches. Opposite the posterior auricular artery a gangliform enlargement is occasionally seen, the so-called temporal ganglion. The branches to the external maxillary artery are numerous, forming an anastomosing plexus which can be traced as far as the angle of the mouth. Most of the plexus appears to be derived from the branch which has hooked around the superior thyroid artery. Small filaments enter the submaxillary gland with the blood vessels, and a few join the submaxillary ganglion. As the external maxillary artery and its accompanying nerves ascend over the mandible, they are crossed at almost right angles by several large branches of the facial nerve which intertwine with these autonomic nerves.

The external carotid plexus continues superiorly to the terminal branches of the artery. Fine rami could be traced for only a short distance along the superficial temporal artery. Along the internal maxillary artery the plexus suddenly breaks up into numerous small anastomosing filaments lying in the dense connective tissue of this region. A few filaments accompanied the middle meningeal artery, and a few descended with the inferior alveolar artery into the alveolar canal of the mandible. No attempt was made to find the external superficial petrosal nerve or to trace branches to the terminal parts of the internal maxillary artery.

The branch which turns around the superior thyroid artery or its hyoid branch is nearly constant. Occasionally, it turns around the lingual artery, and a separate branch descends to the superior thyroid artery. In 4 cases the nerve communicated with the hypoglossal nerve; this was in addition to other connections which were found between the superior cervical ganglion and the hypoglossal nerve. All of Siwe's descriptions of the connections of the ganglion with neighboring nerves as well as his observations that rami communicantes from it are limited usually to the first two cervical nerves, sometimes to three and rarely to four, have been confirmed.

Figure 3 is a diagram of the external carotid plexus plus other branches of the cervical chain. The origin of the vertebral nerve is shown. This is a large nerve arising from the inferior cervical or the stellate ganglion, which crosses the vertebral artery dorsally from the lateral to the medial side. According to Siwe it joins the sixth or the seventh cervical nerve and is a *ramus communicans* almost entirely separate from the plexus along the vertebral artery. This vascular plexus is continuous with the subclavian plexus, and as it ascends along

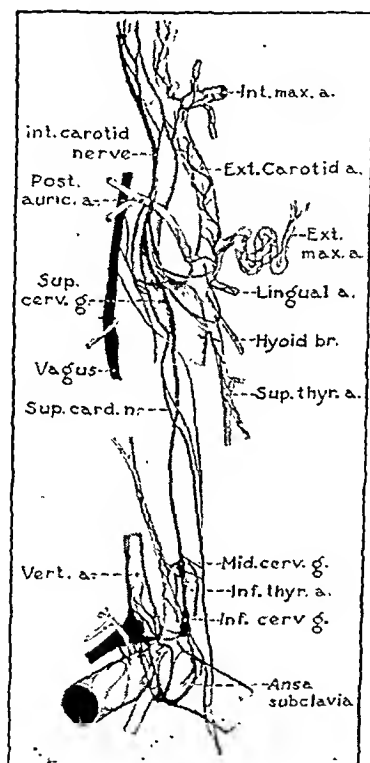


Fig. 3.—A diagram of the external carotid plexus plus other branches of the cervical chain. The structures normally hidden by the arteries are shown in gray. Only the bifurcation of the common carotid artery is shown, and the ascending pharyngeal and occipital arteries have not been indicated. The union of the superior cardiac branches of the vagal and sympathetic trunks is shown. The intercarotid plexus is also shown, but the carotid sinus nerve and other branches of the glossopharyngeal nerve have not been indicated.

the vertebral artery it connects with each of the cervical nerves. Presumably it continues to the basilar artery.

The superior part of the common carotid artery receives a few twigs from the intercarotid plexus. Filaments from the middle and inferior cervical ganglions are also distributed to the common carotid artery and

form a rather sparse plexus. It is not possible macroscopically to trace a continuous plexus along the common carotid artery from its origin to its termination. Nor is it possible to trace a plexus from the common to the external carotid artery. Such longitudinal connections may exist in other vertebrates, but if they are present in man, other methods are necessary to demonstrate them. The superior cardiac nerves are sometimes embedded in the loose connective tissue around the common carotid artery for a part of their course.

#### COMMENT

At first glance it is difficult to understand why axons destined for distribution to the face should descend as far as the superior thyroid artery before returning to the area they supply. The explanation may be embryologic, based on the distribution of axons to the external carotid plexus before the thyroid gland is completely formed. When the gland descends into the neck, this particular branch is carried inferiorly in much the same manner that the recurrent laryngeal nerves are carried inferiorly with the aorta and the subclavian artery. Naturally, the branch passing directly to the external carotid artery is not affected by this descent. The hooking of this nerve around the superior thyroid artery explains Frazier's<sup>4</sup> observation that a ligature applied to the superior thyroid artery may cause pain referred to the trigeminal area.

Periarterial stripping of the common carotid artery near its bifurcation has been done in attempts to relieve atypical facial neuralgia. If the purpose of this operation was denervation of the external carotid artery, then reasons for its failure are obvious. The external and common carotid plexuses are not directly continuous. Even if microscopic connections do exist, the external carotid artery will receive but a small fraction of its total supply from them. Denervation may be possible by periarterial stripping of the external carotid artery near its origin. Cutting the same branches as they arise from the superior cervical sympathetic ganglion will achieve the same results.

Although the autonomic nervous system is involved in the production of pain along the external carotid artery,<sup>5</sup> the sensation of pain is transmitted by nervous pathways to cell bodies the locations of which have not

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4. Frazier, C. H.: Atypical Neuralgia, *Arch. Neurol. & Psychiat.* **19**:650-659 (April) 1928.

5. Davis, L., and Pollock, L. J.: The Role of the Sympathetic Nervous System in the Production of Pain in the Head, *Arch. Neurol. & Psychiat.* **27**: 282-293 (Feb.) 1932. Fay, T.: Atypical Facial Neuralgias: A Syndrome of Vascular Pain, *Ann. Otol., Rhin. & Laryng.* **4**:1032-1062, 1932. Peet, M. M.: The Role of the Sympathetic Nervous System in Painful Diseases of the Face, *Arch. Neurol. & Psychiat.* **22**:313-321 (Aug.) 1929.



as yet been determined with any certainty. Helson<sup>6</sup> studied patients in whom the sensory root of the trigeminal nerve had been sectioned for trigeminal neuralgia. He reported that there remained a perception of deep pressure and of gross changes in temperature which evidently was not transmitted by the facial nerve. It is evident that an understanding of these intricate nervous pathways awaits further and intensive studies by microscopic and experimental methods.

#### SUMMARY

The anatomy of the external carotid plexus plus other features of the cervical sympathetic chain has been studied in 20 dissections in cadavers. Of several branches arising from the superior pole of the superior cervical ganglion, two enter into the formation of the external carotid plexus. One goes directly to the external carotid artery. The other descends, turns sharply around the superior thyroid artery and ascends to anastomose with the previous branch. Filaments from the plexus formed by these two branches accompany all the branches of the external carotid artery.

The external carotid plexus is not directly continuous with the common carotid plexus. The arrangement is such that periarterial stripping of the external carotid artery near its origin would probably denervate the entire artery. The relation of such denervation to atypical facial neuralgia is discussed.

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6. Helson, H.: The Part Played by the Sympathetic System as an Afferent Mechanism in the Region of the Trigemini, *Brain* 55:114-121, 1932.

# FREE GRAFT OVER A VITALLIUM TUBE FOR BRIDGING A GAP IN THE COMMON BILE DUCT OF THE DOG

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In July 1941 Pearse<sup>1</sup> reported on the use of a vitallium<sup>2</sup> tube for the relief of stricture of the common bile duct in a group of 3 patients. His work was first carried out in dogs, and the technic was subsequently applied to human beings. Pearse drew the following conclusions:

1. A vitallium tube does not form stones or deposits in the presence of bile.

2. No pathologic changes occur in the common bile duct as a result of the contiguity of the metal tube.

3. A holder (or flange) attached to the side of the vitallium tube and protruding through the anastomosis is important in preventing the tube from slipping down the common bile duct.

4. The 3 patients in whom it had been used and in whom the ends of the common bile duct were anastomosed over the vitallium tube had remained well clinically.

More recently Pearse<sup>3</sup> made a supplementary report in which he discussed the use of a wide variety of vitallium tubes in benign and malignant strictures of the common duct and reported Zinninger's case of pancreatic fistula cured by implantation of the pancreatic duct over a vitallium tube into the stomach. One significant problem was stated by the author to have remained unsolved, that is, the question of how to bridge a gap in the common bile duct with a vitallium tube. He suggested the mobilization of the duodenum and the pancreas so that the duct could be moved to the hepatic fossa but recognized the fact

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From the Department of Surgery, New York Hospital and Cornell University Medical College.

1. Pearse, H. E.: Benign Stricture of the Bile Ducts Treated with a Vitallium Tube, *Surgery* **10**:37-44, 1941.

2. The approximate composition of vitallium is cobalt 65 per cent, chromium 30 per cent and molybdenum 5 per cent.

3. Pearse, H. E.: Vitallium Tubes in Biliary Surgery, *Ann. Surg.* **115**:1031-1042, 1942.

that this cannot always be done. Clute<sup>4</sup> in a patient with a stricture of the common duct was able to bridge a 2 cm. gap in the duct by bringing the omentum around the bare vitallium tube, the ends of which had been inserted into the separated ends of the common bile duct.

In January 1942 we began a series of experiments in the dog to determine whether a gap in the common bile duct could be bridged by means of a free transplant of peritoneum, vein or fascia over a vitallium tube. After six months of experimentation the following conclusions have been established:

1. Fascia from the anterior rectus sheath makes an ideal graft; in our animals these transplants were satisfactory in 100 per cent of cases.

2. Venous grafts are less dependable; in 4 out of 10 animals there was either significant leakage of bile or absorption of the graft.

3. Peritoneal grafts are not reliable; in 4 of 5 experiments such a graft failed, seeming to vanish by the third week, with the result that there was leakage of bile, obstruction to the duct, or both.

#### METHOD

Twenty-four normal mongrel dogs were operated on under anesthesia induced with soluble pentobarbital U. S. P. (pentobarbital sodium), and a graft from one of three sites was fashioned into a cuff around a straight vitallium tube (fig. 1). Two sizes of tubes were used, and in some instances there was a holder attached (fig. 2). An upper right rectus incision was used, and fascial grafts were taken from a strip in the anterior rectus sheath. A segment of the right femoral vein was used for the free venous transplants, and a strip of parietal peritoneum was taken from the edge of the wound when peritoneal grafts were used. Arterial silk was used as the suture material in all experiments.

The animals were killed at approximate intervals of fifteen, thirty, sixty and ninety days postoperatively. A few of the dogs died of bronchopneumonia during the first two postoperative weeks, and exploratory operations were performed on 2 animals at the end of the first week. Specimens of the common bile duct with the graft and vitallium tube were examined grossly and microscopically.

In general, fascia is easy to handle and can be fashioned without difficulty into a snugly fitting cuff around a vitallium tube. A continuous arterial silk suture was used to approximate the fascial edges. Lateral slits were made in the fascia at the holder in order to obtain a satisfactory approximation. In some animals the fascia was anastomosed to the common bile duct with three stay sutures and then the edges were joined by a continuous silk suture from stay to stay. In 1 dog stay sutures only were used, and they proved perfectly adequate.

#### TYPICAL PROTOCOLS

Dog 1.—A female animal weighing 53 pounds (24 Kg.) was subjected to a fascial graft over a small vitallium tube with a holder on March 16, 1942. The postoperative course was uneventful, the stools being brown on all occasions, and

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4. Clute, H. M.: *Bile-Duct Reconstruction with Vitallium Tubes: Report of a Case*, New England J. Med. 226:484-487, 1942.

no icterus was noted at any time. On the fortieth postoperative day the animal gave birth to a litter of four puppies. After the puppies had been weaned the dog was killed on the ninety-third postoperative day, while in a state of excellent health. Autopsy showed the vitallium tube to be in place without evidence of encrustation or deposits. The fascial graft had healed well, and there was no significant dilatation of the hepatic ducts above the operative site.

Dog 2.—A male animal weighing 49 pounds (22.2 Kg.) was operated on on Feb. 10, 1942, and a fascial graft over a large vitallium tube with a holder was carried out. The dog remained in excellent health, and on May 12, 1942, the

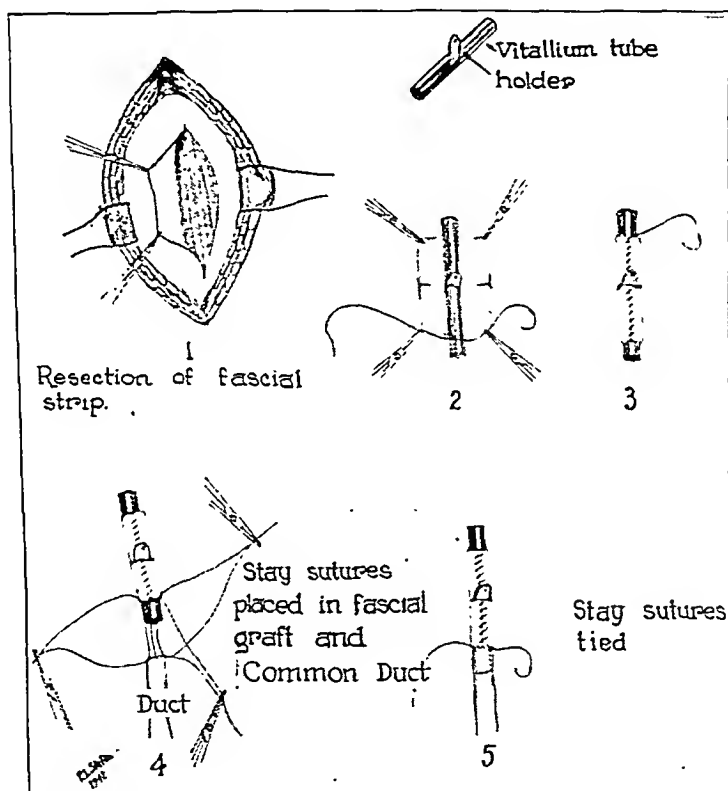


Fig. 1.—Diagram showing the various steps in the construction of a fascial graft and its anastomosis to the common bile duct over a vitallium tube with holder: 1, a strip of fascia is resected from the anterior rectus sheath. 2 and 3, the fascial strip is fashioned into a cuff around the vitallium tube by means of a continuous arterial silk suture; lateral slits are made at the point where the holder penetrates the cuff. 4, stay sutures of arterial silk have been placed through the end of the common duct and fascial graft. 5, the anastomosis of one end of the duct to the graft is completed by means of a continuous arterial silk suture; it was found that the continuous suture was not necessary.

ninety-first postoperative day, the common bile duct was resected and a cholecystogastrectomy performed. There was no dilatation of the common bile duct, and

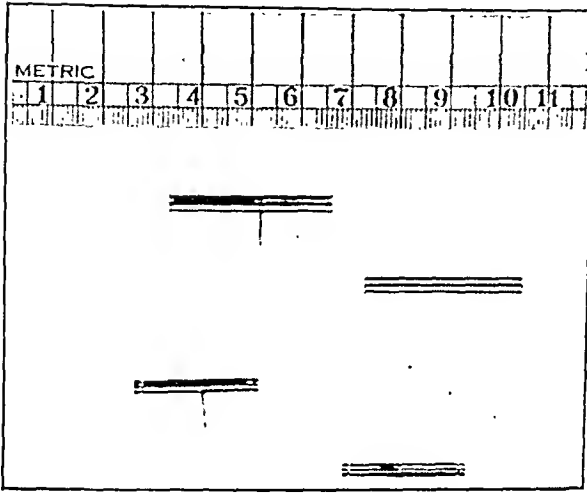


Fig. 2.—The two sizes of vitallium tubes used in this study. A holder was attached to some of the tubes.

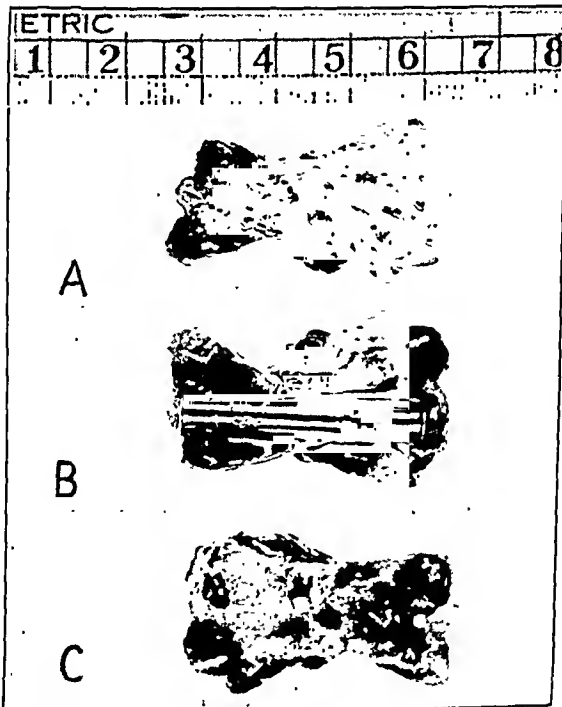


Fig. 3.—*A*, the resected common bile duct with fascial graft is viewed externally. *B*, the specimen has been opened with the vitallium tube in situ. *C*, the vitallium tube has been removed, and the fascial graft is evident between the ends of the common duct, which are glistening. Some of the silk sutures are visible.

the fascial graft had healed perfectly. It had shrunk in length, however, being only 6 mm. long instead of the original 12 mm. The vitallium tube had discrete areas of yellowish brown, granular, soft deposits both on the outside and on the inside. These deposits, which measured 1 mm. in thickness, could easily be scraped

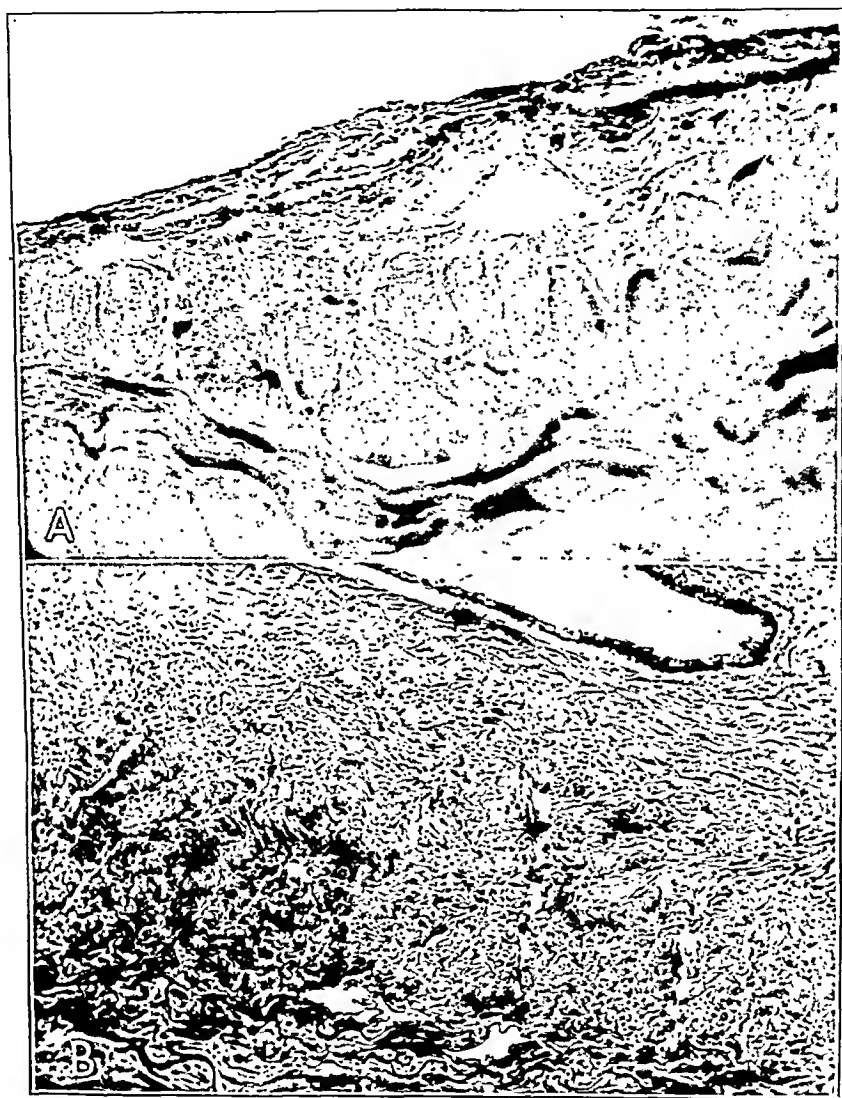


Fig. 4.—*A*, photomicrograph of a fascial graft of dog 2, showing no epithelium on the inner surface. *B*, photomicrograph of a venous graft, showing the columnar epithelium to line its inner surface. At the bottom of the film elastic fibers are in evidence.

away (fig. 3). A photomicrograph of the specimen revealed that no epithelium had grown along the graft to line its inner surface. This finding is in contrast to

the experience with venous grafts, in which epithelium does line the vein in some cases (fig. 4).

# RESULTS

*Fascial Grafts.*—There were 9 dogs in this group. In every instance the fascial graft took satisfactorily, and at no time was there any evidence

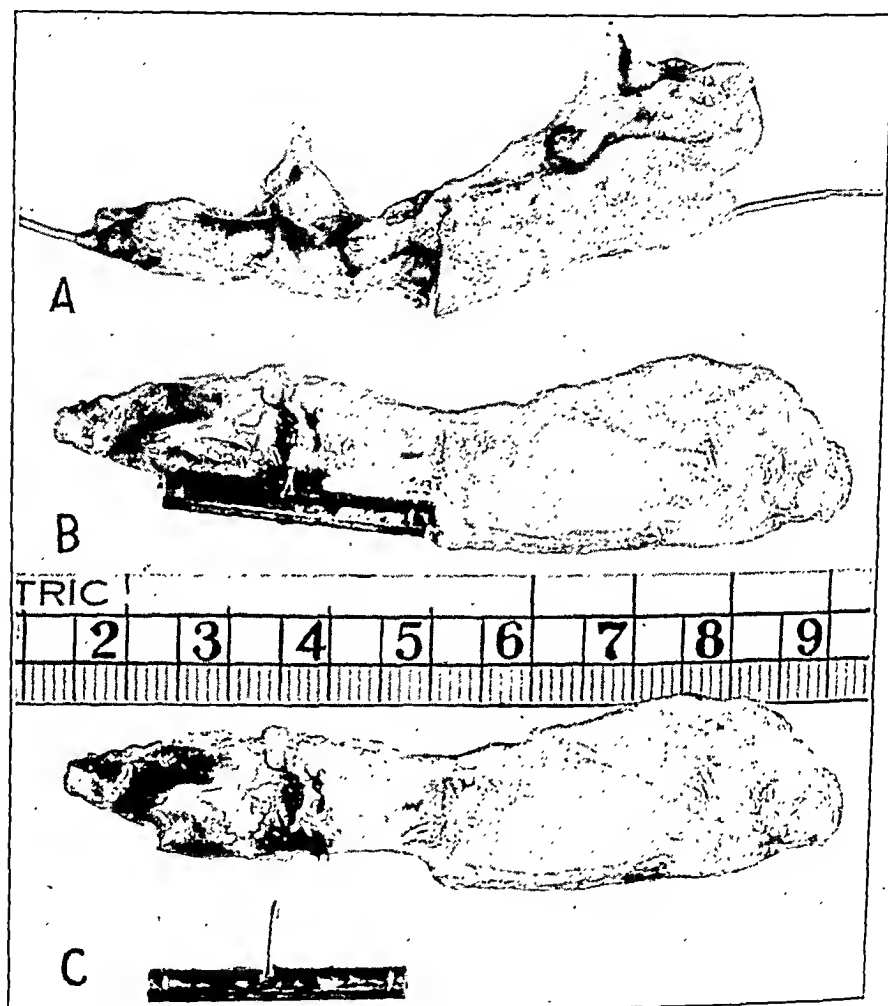


Fig. 5.—*A*, the specimen includes the common bile duct and the wall of the duodenum. A probe passes from the ampulla of Vater through the duct. The holder of the vitallium tube can be seen. *B*, the specimen has been opened, and the venous graft has evidently shrunk to 2 or 3 mm. The two rows of silk sutures are in evidence. *C*, the vitallium tube has been removed and is free from deposit. The mucosa of the common duct is glistening and shows no evidence of trauma caused by the vitallium tube.

of biliary leakage. In 2 dogs stricture of the fascial graft developed because of slipping of the vitallium tube. Epithelization of the graft did not occur in any animal.

*Venous Grafts.*—In 10 dogs a graft from the femoral vein was used to bridge a gap in the common bile duct over a vitallium tube. Of the 4 dogs in which the procedure was not successful, in 2 a slough of the venous graft developed, with subsequent obstruction to the common bile duct, and in the other 2 leakage of bile occurred during the first post-operative week, resulting in walled-off collections of bile. In these 2 animals the venous graft, in spite of careful suturing, became loose around the vitallium tube, with the result that gross apertures were evident. On the other hand, in the remaining 6 dogs no jaundice or leak developed, and the animals maintained a state of good health throughout the experiment. During the postoperative period 5 of the 6 animals were killed, 1 after two weeks, 3 after two months and 1 after ninety-two days. The grafts had taken well, and the only outstanding abnormality was that in 2 of the 5 grafts a pronounced shrinkage had occurred in the vein, so that the two suture lines had practically joined, being only 2 mm. apart (fig. 5). Microscopic study revealed that epithelization did occur over the inner surface of some of the venous grafts during the first ninety-two postoperative days.

*Peritoneal Grafts.*—In 5 dogs peritoneal grafts were made in a similar fashion, and in 4 animals the graft sloughed, with consequent leakage, peritonitis and death. The remaining graft was examined at the end of two weeks, and it appeared to be normal.

#### COMMENT

Most patients with strictures of the common bile duct will be amenable to the insertion of vitallium tubes with end to end anastomosis of the duct over the tube, but there will be an occasional case (for example, case 2 in Pearse's original paper<sup>1</sup> and Clute's case<sup>4</sup>) in which the surgeon will not be able to bring the ends of the duct into apposition, and it will be this group of patients in which a fascial graft over a vitallium tube with a holder should be employed. The greatest length of the graft possible remains a matter of speculation since in all of the dogs the length of the graft was limited by the length of the tube, because the ends of the vitallium tube must protrude beyond the graft, and hence beyond the two anastomotic lines. Therefore the grafts in these experiments varied between 1 and 2 cm. in length. Elsewhere<sup>5</sup> fascial grafts 4 cm. long have been used to bridge a gap in the jejunum over a vitallium tube 6.5 cm. long.

In the urinary tract, fascial grafts become lined with transitional epithelium,<sup>6</sup> but in none of the fascial grafts of the common bile duct did the epithelium grow down to line the inner surface of the graft.

5. Lord, J. W., Jr., and Stefko, P. L.: Unpublished data.

6. Lord, J. W., Jr.; Stefko, P. L., and Stevens, A. R.: On Bridging a Gap in the Ureter by Means of a Free Fascial Transplant over a Straight Vitallium Tube: An Experimental Study. *J. Urol.*, to be published.



The vital importance of employing a vitallium tube with a holder is evident in view of the stricture which occurred in a dog in the series some twenty days postoperatively; the tube had passed into the duodenum early in the postoperative course. Tubes without holders were used in 14 animals, and obstructive jaundice secondary to slipping of the tube and stricture formation occurred in 4.

In 2 instances in this series of experiments, once in a fascial graft and once in a venous graft, the vitallium tubes showed yellowish brown amorphous deposits 1 mm. thick. In neither case did the deposits cause obstruction to the flow of bile. In the animal in which fascia had been used the tube was examined ninety-one days postoperatively, while in the dog with the venous graft the specimen was examined on the sixty-sixth postoperative day. Dr. Pearse informed us<sup>7</sup> that in no case has he ever found any deposits on a vitallium tube, and his experiments were continued for two years on dogs and for nine months on a human subject. We are at a loss to explain the deposits on the vitallium tubes in 2 of our dogs. Whether they would have eventually accumulated to the point of complete occlusion of the tube is a matter of conjecture. Clinical experience, as it enlarges, may confirm this finding as an unfortunate though unusual occurrence.

The principle of the permanent rigid tube to prevent the recurrence of a stricture, as established by Pearse, is a sound one and is a significant advance in the operative treatment of stricture of the common bile duct. However, even though vitallium far surpasses any other substance heretofore employed for this purpose, it may be hoped that some substance will be found which will be more pliable and even more inert.

#### CONCLUSIONS

1. By means of a free fascial graft from the anterior rectus sheath, fashioned into a cuff around a straight vitallium tube with a holder, a gap in the common bile duct of the dog can be bridged with uniform success.

2. Venous grafts are only moderately successful, for in 40 per cent of the animals used in the experiments reported here bile leaked during the first week after operation and/or sloughing of the graft with formation of a stricture occurred. Also, venous grafts which take satisfactorily tend to shrink more rapidly and completely than fascial grafts.

3. Free peritoneal grafts should not be employed, since they sloughed in 4 out of 5 instances.

The Austenal Laboratories, New York, through Mr. J. J. Erdmann, supplied the vitallium tubes used in these experiments.

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7. Pearse, H. E.: Personal communication to the authors.

# OPERATIVE TREATMENT OF CANCER OF THE LARGE BOWEL WITHOUT COLOSTOMY

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AND

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Carcinoma of the large bowel is the second most common and the most curable of all internal cancers. Although it is usually easier to diagnose than other internal cancers, delay in recognition and radical treatment makes it responsible for about one fourth of all deaths from malignant disease. Over 60 per cent of cancers of the large bowel may be accurately and instantly diagnosed by palpation with the finger or by inspection through a proctoscope, yet a large percentage of patients are treated for other conditions because these simple examinations are not made. Commonly a roentgen examination is ordered, which usually fails to delineate a cancer of the pelvic colon. On the basis of this negative evidence, the patient then may be treated for hemorrhoids, anal fissure, colitis, prostatitis, spastic colon or other conditions until he falls into the hands of some one who is perhaps less scientific but who first of all depends on an examining finger. Unfortunately, most of the lesions now seen by surgeons have long passed the early papular or polypoid stage, and their malignancy is clearly obvious without biopsy. With earlier diagnoses, which entail more attention to the less conspicuous lesions, the rate of curability of intestinal carcinoma could be doubled.

At this time we wish to discuss particularly the morbidity of operations for malignancy of the large bowel. Unquestionably, the greatest mental distress and physical discomfort that follow the operation are due to colostomy. The first question the patient usually asks is, "Will I be left with an intestinal opening on my abdomen for the balance of my life?" Surgeons tend to be ritualists and to follow the operative pattern of the period. They leave an ugly abdominal scar because a McBurney or a Bassini introduced the incision. For years a colostomy with any proctosigmoidectomy has been sacrosanct. In defense of the pattern it must be admitted that an operation for cancer

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of the lower part of the bowel which does not leave the patient with a colostomy opening cannot be approved fully unless one is assured that it will not markedly increase the mortality, that it will be equally radical and that the perineal opening will be found advantageous after the operation.

Does colostomy necessarily reduce the danger of the operation? Recent mortality statistics from various clinics where colostomy is an essential part of the operation, although not entirely comparable, suggest that the colostomy does not add to the safety of the operation. Since 1930, when we began to eliminate routinely establishment of a permanent abdominal colostomy opening in operating for removable carcinoma of the large bowel, we have had 367 operations for this condition on patients from 23 to 88 years of age. Two hundred and eight were single stage resections for carcinoma of the rectosigmoid or anus. These include 99 abdominoperineal proctosigmoidectomies, 99 perineal proctectomies or proctosigmoidectomies and 9 resections with primary end to end anastomosis. Nearly all were one stage procedures. Of the 208 patients, 24 died in the hospital, a mortality of 11.6 per cent. In 1939 technical improvements came into routine use, including improvements in anesthesia, use of nonirritating suction or of dependent drains and modifications to insure a more functional anal opening. One hundred and sixty-one patients have had operations for cancer of the large bowel since 1939, with 11 deaths in the hospital, or a mortality of 6.8 per cent. Ten, or 6.2 per cent, were found to have inoperable lesions; 150 (93.3 per cent) had radical resections. Twenty of those on whom resection was done had early metastatic carcinoma of the liver; 4 had invasion of the small intestine, 6 of the uterus and others of the ureter, vagina, prostate or abdominal wall, requiring resection or removal. One hundred and seven had resections involving the pelvic colon, with 7 deaths, a mortality of 6.5 per cent.

If the colostomy is essential to render an abdominoperineal proctosigmoidectomy radical, then it should not be possible after the operation to move the colostomy fistula to the perineum. In 12 patients we have found no especial difficulty in moving to the perineum the opening left after a Miles operation or some other procedure. With the exception of a feeble man of 74 with metastatic carcinoma of the lung who died in the hospital after a stage operation, all these patients recovered from the operation. Our observations have convinced us that operations without an abdominal colostomy may be fully as radical as those routinely done with it. Of 100 patients traced after leaving the hospital, 81 lived one to five years or more, 38 five to ten years and 19 ten years or more.

Is the perineal opening, even without sphincter control, worth while? Our best evidence comes from the 11 patients for whom an abdominal colostomy fistula has been moved to the perineum after it had been

present from a short time up to eleven years. From these patients we have learned that the discharge of offensive gas is much less evident from a perineal opening, even when the anus and sphincters have been removed. Apparently this is due in part to compression by the buttocks. The patients tell us that the perineal opening is more convenient and easier to care for and that evacuations are more satisfactory and less frequent. A physician who had had a Miles operation performed eleven years before was so troubled by the noisy escapes of odorous gas every time he bent over that he carried with him an irrigating outfit so that he could empty the bowel several times a day, and finally contemplated suicide. He left the hospital ten days after the transplantation operation and reports that he now can go about without a pad or other protection and that it is necessary to irrigate the lower part of the bowel only once in two or three days. A second patient had lost her position in a bank on account of the odorous gas escaping from the colostomy opening. The transfer of the abdominal opening to the perineum overcame this handicap. A laundress was refused work on account of the abdominal opening. A fourth patient had extreme intestinal prolapse and hernia associated with the colostomy opening, which required hours of attention daily. In a woman of 26 the colostomy had introduced a problem in connection with her approaching marriage. The transfer of the opening has probably relieved a marital problem for others. Each one of the 11 patients considered the transplantation of the fistula to the perineum of great advantage.

Five to 10 per cent of patients with a perineal colostomy opening without sphincter control require no local protection or change in diet except during periods of diarrhea. To limit soiling, about 85 per cent require an emptying of the colon by an enema or a quickly acting laxative every third or fourth day. By this expedient the majority dispense with use of a protective pad most or part of the time. However, with over 85 per cent of cancers of the large bowel the pelvic floor is not involved, and a functional anus with its sphincters may be retained safely instead of being sacrificed, as in the conventional operations now used. Many observations indicate that the lymphatic extension of cancer of the rectosigmoid is cephalad, not caudad. While a wide removal of intestinal and lymphatic tissue is imperative on a level with and proximal to the growth, a much less extensive resection below the tumor is required. Therefore, with a rectal carcinoma 7 cm.<sup>1</sup> or more above the pelvic floor, the anus and functional sphincters may be retained.

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1. Some authors (Westhues, H.: *Die pathologisch-anatomischen Grundlagen der Chirurgie des Rektumkarzinoms*, Leipzig, George Thieme, 1934. Gilchrist, R. K., and David, V. C.: *Lymphatic Spread of Carcinoma of the Rectum*, *Ann. Surg.* 108:621 [Oct.] 1938) present evidence for 5 cm. as the limit of safety.

In any case, the abdominal liberation of bowel, mesentery and lymphatics resembles that of the Miles operation, except that a left oblique inguinal incision usually is employed. To reduce the bulk of tissue to be delivered through the perineum and to afford space for the formation of a pelvic diaphragm, the liberated bowel may be divided by cautery between double clamps of the de Martel type and removed. With cancers low in the pelvis this is not feasible, and there is tied about the loop of freed bowel at the level to be used for the perineal anus a folded gauze tape, the ends of which are packed against the floor of the pelvis before the abdomen is closed. It is essential that sufficient vascular sigmoid be liberated (12 cm., or 5 inches) to reach from the posterior pelvic brim through the perineum. Viability is determined by observing pulsating arteries or by the character of bleeding when the small vessels on the surface of the bowel are incised. If necessary, the descending colon is slid to a lower position, after its lateral peritoneal leaflet has been divided. If the bowel is resected between clamps through an abdominal incision, the proximal and distal ends are encased in stockinet tubing and placed on the floor of the pelvis, a pelvic diaphragm is formed, and the abdomen is closed. With the patient in lithotomy position, an anterior perineal delivery of the ends of the bowel through an incision of the Young prostatic type gives a better anal opening, since the bulk of the anal muscles lies posterior to the anus. This incision also facilitates the resection of an invaded prostate. Through the opening anterior to the anus the stockinet ends are grasped and used to deliver the ends of rectum and sigmoid. The lower end of the rectum is divided by cautery just above the sphincters. A Payr clamp is passed through the anus and caused to grasp the sigmoid above its clamp, which is burned off by cautery. The Payr clamp and end of the sigmoid are withdrawn through the anus, and the perineal incision is closed with interrupted layer sutures of fine alloy steel wire. Through a median stab wound near the tip of the coccyx a curved, perforated glass sacral drain is inserted (fig. 1). If the rectum is attached posteriorly, a median cutaneous incision is made from the posterior border of the closed anus and deepened along the side of the coccyx into the pelvic cavity. The stockinet covering the clamped ends of the bowel is then grasped, the bowel is liberated and the ends are pulled through the perineum. The aseptitized rectal end is divided by cautery just above the sphincters, the anus is split posteriorly and the end of the sigmoid laid in the anal groove. A perforated curved glass drain is inserted along the sacrum, to be removed after twenty-four hours, and the perineal wound is partly closed with buried and superficial sutures of 32 B. & S. gage alloy steel wire (fig. 2).

A variation of the operation is to pull through the perineum the unopened loop of rectosigmoid by a tape previously tied about the sigmoid

at the level where the new anus will be formed. The posterior incision leaves an anus of keyhole shape which in two months or more may be improved, if desired, by turning forward a U-shaped flap formed exter-

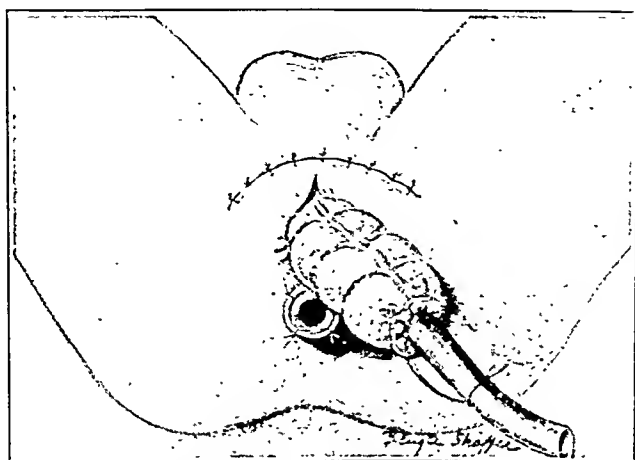


Fig. 1.—The rectum and part of the sigmoid have been liberated and resected between short clamps through an abdominal incision, and the clamped ends have been delivered and further resected through an anterior curved perineal incision. The sigmoid end has been brought through the anus, which has been split anteriorly, and a rectal tube has been tied in. A perforated curved glass drain is inserted along the sacrum through a stab wound at the right side of the coccyx.

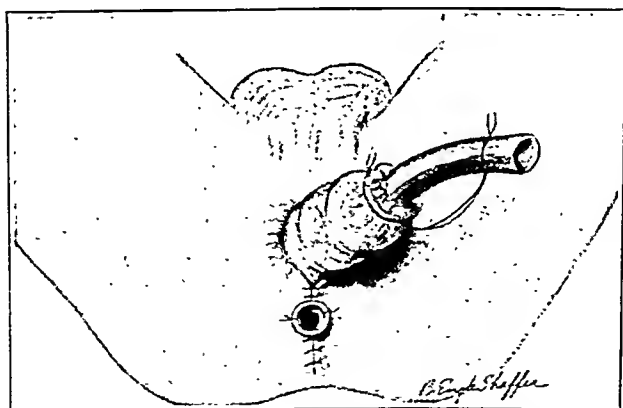


Fig. 2.—The loop of cancerous rectum and sigmoid liberated through the abdomen has been delivered through a midline post anal perineal incision. This loop of bowel has been divided through the sigmoid and also just above the sphincters, the sigmoid end has been placed in the gutter formed by the split anus and a rectal tube has been tied in.

nally along the posterior cutaneous margins of the exposed sigmoid. The sphincters, perineal muscles and skin are united under the flap with interrupted wire sutures. If an anterior spur has formed where

the sigmoid joins the anus, this should be split anteriorly and sutured before the U-shaped flap of bowel is raised. Except when a plastic operation is performed a rectal tube is tied in the protruding sigmoid, which should not be sutured to the perineum. A week later, when adhesions have formed, the protruding insensitive end of the sigmoid is burned off by cautery. The patient often is out of bed by the sixth day and in condition to leave the hospital by the twelfth or the fourteenth day.

For low-lying anal and rectal cancers a wide excision of the pelvic floor is made, and the withdrawn sigmoid is placed in the position of the anus. Such a perineal or posterior resection is a useful operation for the aged and very obese and for some patients with involvement of the vagina and prostate. It has the great disadvantage that it is difficult after any extensive perineal rectosigmoid resection to bring the divided end of the bowel to the perineum without interfering with its blood supply. As a result there is danger of pelvic infection, and a retracted and cicatricial bowel opening often forms.

The preservation of the sphincters is more difficult with the perineal resection and, of course, is not to be attempted for a low-lying carcinoma. We have preserved functional sphincters by using an interrupted long medial perineal incision to expose the rectum just above the sphincters, the rectum being divided between ligatures. The first incision is then completed vertically through the anus, the margins retracted and the rectosigmoid widely liberated and delivered through the split anus. This procedure is followed by reconstruction of the perineum with drainage. In all these operations a preliminary careful cleansing and packing of the rectum with antiseptic gauze is employed.

A secondary perineal hernia, for which a plastic operation may be done if the condition is annoying, develops after excision of the pelvic floor in about 5 per cent of perineal excisions. A moist opening from mucous prolapse may be corrected by linear cauterization, which may be done nearly painlessly as an office procedure. If there is a tendency to contraction of the new opening, the patient is given a set of test tubes to be used as dilators.

For resections of the colon above the pelvis, our present tendency is toward resection with end to end anastomosis and complemental appendicostomy or enterostomy well proximal to the anastomosis. With the development of nonirritating suction drains for the peritoneum and a satisfactory one clamp method of end to end anastomosis with fine alloy steel wire sutures, the mortality subsequent to the anastomosis now compares favorably in our experience with that associated with the Paul-Mikulicz exteriorization procedure, while the morbidity is much less. Probably it is a little more dangerous for resection of the sigmoid and rectosigmoid, but it surely seems safer for the right and transverse portions of the colon, where a modified Mikulicz procedure has given a

mortality of 16.6 per cent in expert hands. From 24 recent consecutive aseptic end to end anastomoses there were 2 deaths, or a mortality of 8 per cent. One patient with carcinoma of the cecum, a man of 73, died of an intravenous reaction, and the second had renal suppression, hematuria and ileus without leakage or peritonitis. Several of the patients who recovered were over 70, and one was 85. One had a resection of a cancerous stomach and transverse colon with intermediate abscess; 1 had a combined end to end resection of cancerous jejunum and transverse colon, and a third had a resection from the proximal portion of the transverse colon to the sigmoid with a large resection of abdominal wall containing an abscess from a perforated carcinoma of the splenic flexure. Such one stage resections were formerly considered very dangerous, but now, when performed with careful attention to detail, offer a superior result, especially with elderly, debilitated patients, who often cannot withstand prolonged confinement to bed and repeated operations. The loop of cancerous colon, with attached peritoneal folds, mesentery and lymphatics, is liberated. The arms of the loop, wide of malignant tissue, are alined by lateral guy sutures and divided between Payr or short clamps by cautery. This leaves the distal and proximal ends of the colon crushed together in a single clamp, which is turned over. Two or three rows of seroserous sutures are then introduced. the clamp is rotated back to its former position and a continuous Cushing suture is introduced anteriorly over it. As the clamp is partly opened and withdrawn this suture is tightened, inverting and closing the anterior edges of the bowel without leakage. One or two anterior outer rows of interrupted seroserous sutures of 36 B. & S. gage alloy steel wire are inserted, corresponding to those introduced on the posterior side. The fine wire is used universally on peritoneal surfaces, since it does not lead to peritoneal adhesions, as does catgut or silk. Care should be taken to use only viable ends of bowel for the anastomosis, to have the sutured surfaces denuded of all fat and carefully apposed so as to be absolutely gas and water tight and to do an associated complemental appendicostomy or enterostomy. With the Mikulicz operation, as with any colostomy, there are a certain number of deaths from spreading pyoderma and other complications, and often, even when a muscle-splitting incision is used, a weak area is left in the abdominal wall.

The lowest mortalities from resection of the colon in recent years have been reported by operators who have become adept in a single stage operation. In our experience, even when it has been necessary to resect in addition a portion of infiltrated bladder, abdominal wall, ureter, stomach, adjacent intestine or vagina or to remove the uterus and appendages, we have found the single stage operation of advantage. In recent years we have not found it necessary to compromise one of these prolonged, complicated single stage operations on account of the



shock or unfavorable condition, and none of the patients in whom multiple resections for malignant extensions were possible has died of the operation.

A four clamp method facilitates the removal of the ileum, uterus or other organ to which the cancerous colon has become attached. Two light clamps are applied on each side of the bowel lateral to the growth, and the colon is divided by cautery between each pair of clamps. This leaves the diseased intestinal segment attached to the uterus or other organ, which is then removed or resected. The distal and proximal clamps are now apposed over a single Payr clamp and burned off. The end to end aseptic suture is then completed over the single clamp, as previously described (fig. 3).

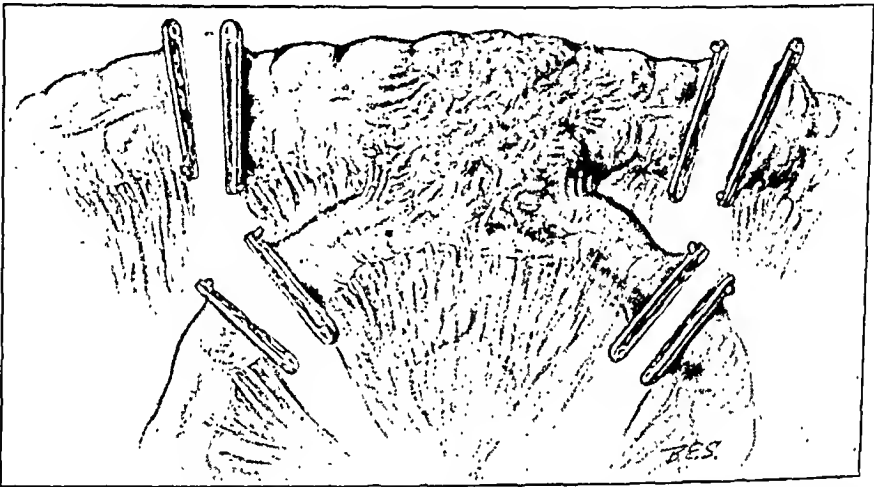


Fig. 3.—Use of eight short clamps as in a combined aseptic resection of colon and jejunum for infiltrating carcinoma or jejunocolic fistula. The clamps have been applied and the segments divided by cautery.

When the cancer has invaded an adjacent loop of small intestine, it usually is feasible to fold the intestinal loop together and then apply two Payr or de Martel clamps obliquely across the base of the loop, which is divided by cautery between the two clamps. A similar operation may be used when a cancer of the transverse colon has invaded the stomach. Again, adhesions or other condition may render an eight clamp double resection desirable. Here the small and the large intestine are resected, each with four clamps, as previously described (fig. 4).

In resections of the colon above the sigmoid, including the ileocecum, for a number of years we have used only end to end anastomoses. By apposing an oblique section of the smaller ileum to a transverse section of colon, a satisfactory end to end union may be made. A side to side anastomosis is a longer and more complicated operation; the blind ends

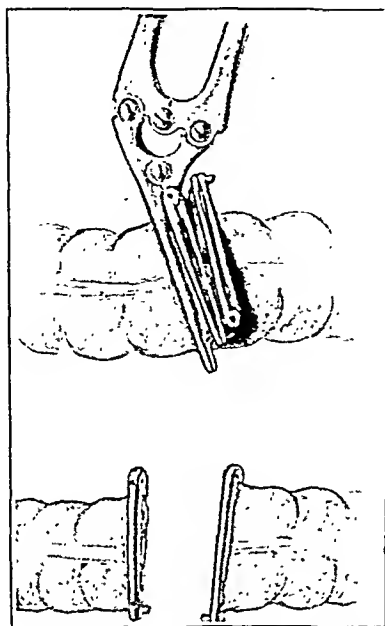


Fig. 4.—Method of end to end anastomosis over a single clamp after the diseased adherent segment shown in figure 3 has been removed. The clamped ends of bowel are alined and clamped together by an underlying Payr clamp, and the ends are burned off by cautery. This leaves the ends of the bowel in the grasp of the single Payr clamp in position for an aseptic end to end suture.

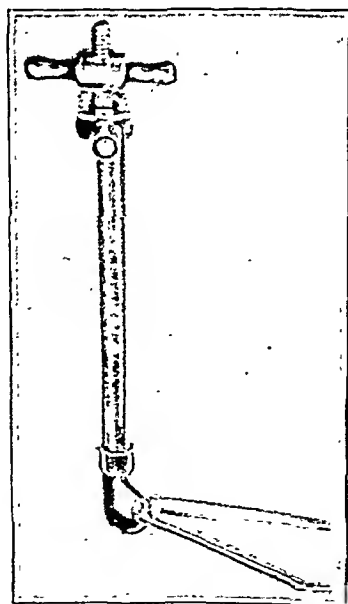


Fig. 5.—Removable clamp holder desirable for manipulation of the short clamps in the depths of the abdomen.

may become distended with fecal material and may even open under reversed peristaltic pressure.

When the cancer has invaded the anterior abdominal wall, this may be resected en bloc with the diseased segment of bowel. Even when the colon has perforated into the abdominal wall with the formation of a localized abscess, the en bloc resection should be used if possible. In 1 case a large carcinoma of the splenic flexure had perforated into the abdominal wall; it had been drained for four months elsewhere and then closed, to recur three months later. Even then it was possible to resect the transverse and the descending colon with a large segment of abdominal wall, enclosing the abscess, and to perform an end to end aseptic anastomosis between the proximal portion of the transverse colon and the sigmoid over a single clamp (fig. 5). Primary union followed, with the exception of a minute and transient sinus. While a complementary enterostomy is less often required after resection of the right side of the colon, it will prove life-saving in certain cases, and at present is our routine practice.

#### SUMMARY

An experience of over 200 operations for cancer of the lower part of the bowel, performed in one stage without abdominal colostomy, has shown that such operations may be done with a relatively low mortality and with satisfaction to the patients.

In over 85 per cent of the patients a functional anus may be preserved without destroying the radical nature of the operation.

An experience of 12 operations has shown the feasibility of transferring to the perineum an abdominal colostomy opening left by a previous operation.

The transfer of the colostomy fistula has enabled patients to become acceptable for professional and office work, for household duties and for marriage.

Plastic procedures for restoring function to the damaged anal sphincters are described and illustrated.

The Mikulicz procedure often may be supplanted with advantage by a more accurate one stage aseptic anastomotic operation, for which a single clamp method is described. In resections of the abdominal colon, the routine use of suction drainage and complementary enterostomy or appendicostomy and of nonirritating metallic sutures has been found of advantage.

#### ABSTRACT OF DISCUSSION

DR. LOUIS J. HIRSCHMAN, Detroit: I should like to say a word of commendation for Dr. Babcock and a few others who still feel that some patients suffering from carcinoma of the large bowel have the right to choose where the site of the colostomy may be located, provided that it does not in any way interfere with their ultimate recovery. I happen to be one of a very small group

who still feel that a patient can have a colostomy in the normal site and live just as long as if he had a colostomy on the abdomen, provided that the procedure in each case is well selected.

Those of you who will live longer than I shall will see the time come when more and more perineal colostomies and implantations into the perineal region will be done, and some time I hope that sphincters will again be able to function in persons who have had carcinomas excised.

DR. FRANK H. LAHEY, Boston: One can easily lose sight of certain things, the most important of which is that, given enough experience, a surgeon will select the type of operative procedure with which he has had the greatest success. This applies particularly to where one places the colostomy. Both Dr. Babcock and Dr. Hirschman have had a large experience, and they can select any type of procedure they choose and probably get very good results.

With regard to our own experience, I can only say that my associates and I like the abdominal colostomy. We like it for the reasons that we can even mobilize the splenic flexure and, if we wish, bring it down to the colostomy opening and that we can remove large segments of gland-bearing area and long segments of bowel above the lesion. We have not infrequently had to mobilize the splenic flexure, and we can feel sure that when implanted on the abdominal wall the blood supply of the terminal end of the colostomy opening is adequate and intact. We feel that an opening is more hygienic and easily cared for in the abdominal wall where one can get at it than anywhere in the perineum or posteriorly. Having seen over 1,300 carcinomas of the colon and rectum, with an operability rate of between 80 and 90 per cent, a mortality rate of 10.25 per cent and an average nonrecurrence rate of 50 per cent, we feel that such lesions offer great prospects for a high five year nonrecurrence rate and therefore must be approached as aggressively as possible.

There are certain basic things to remember about a colostomy. So many people are unhappy even to consider the question of colostomy because nearly every one—patients, practitioners and many surgeons—thinks of it only in terms of the palliative colostomy. This, of course, is a proper unhappiness, because everything that is said about a colostomy when it is a palliative one is true. The lack of control of the movements and of the blood and pus is not the result of the colostomy but is largely due to the unremoved lesion.

No matter where one does a colostomy there is no sphincter-like action which produces control. It can never be controlled mechanically. It is controlled dietetically, by teaching a person to constipate himself and by letting the colon have time to habituate itself to the fact that a new segment has taken on the function of the anal reservoir, and also by establishing the fact in the patient's mind that the bowel no longer moves voluntarily but that defecation is accomplished by irrigation every second or third day.

We are very careful not to discharge a patient after colostomy, but to keep in touch with him for six months. If he has colostomy accidents (soiling) it is during the time when these are occurring that he loses his morale and needs reassurance. If he has two or three bad experiences he will be so discouraged that it will be difficult to keep him enthusiastic and interested in his diet and proper handling of his colostomy opening. The patient learns during this time to handle any loose movements with paregoric and that he cannot take liberties with his diet or he will have loose movements which will be distressing to him. He learns that it is necessary to take plenty of time for his irrigation, to take time getting the catheter in—in fact, during this time he learns all the measures for successful management of his colostomy opening.

We have learned, in addition, that in certain persons keloid scars develop about the colostomy fistula and that if they do not insert the third finger, down to the middle knuckle, through the opening every time they irrigate it, it will so contract that it will interfere with the successful removal of feces. None of our patients wears a bag. If a patient learns how to constipate himself and how to handle his colostomy opening, he needs only a piece of gauze and an elastic belt about the abdomen.

I feel certain that if we could disseminate throughout the country the knowledge that a colostomy performed after the lesion is removed is an utterly different problem from a colostomy done as a palliative measure, we should then avoid the frequent fear and objection to a colostomy, hesitation about accepting the operation and unwise and undesirable delay.

DR. W. WAYNE BABCOCK, Philadelphia: As the functional usefulness of the sphincters after these extensive operations has been questioned, Dr. Bacon and I are here showing in motion pictures a series of patients who after the operation are voluntarily contracting and relaxing the perianal muscles. The pictures demonstrate that the sphincters may still be functional after radical removal of 45 to 65 cm. of bowel. Most of the patients shown have had single stage abdominoperineal resection, and 1 a posterior perineal resection. One had the less desirable keyhole type of opening after a postanal delivery of the sigmoid, which now has been corrected by plastic operation. The anterior perineal withdrawal of the liberated bowel gives the most direct opening through the anus and has the advantage of not dividing the posterior, i. e. the thicker and more important, part of the sphincter muscles. In our series all but 2 of the operations have been performed in a single stage. With modern anesthetic methods, shock is rarely a problem, even in prolonged and complicated intestinal resections.

A very radical removal of rectosigmoid may be done with little perineal evidence of the operation and with retention of a degree of control of gas, good control of solid fecal material and, perhaps at most, leakage only during diarrhea.

An important problem of colostomy, which is lessened by the perineal opening, is the control of offensive gas, which may cause the patient to lose his position.

## TRAUMATIC HEMORRHAGE OF THE INTERNAL CAPSULE

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The existence of traumatic intracerebral hemorrhage is generally conceded, yet the finding of a blood clot in the region of the internal capsule at autopsy is ordinarily accepted as positive evidence that the lesion represents a spontaneous hemorrhage. If signs of trauma are present, the temptation is to consider such trauma as secondary to the unconsciousness and fall resulting from the apoplexy.

Courville and Blomquist,<sup>1</sup> in a discussion of traumatic intracranial hemorrhage, presented 38 instances occurring among 439 cases of fatal craniocerebral injuries. Only 7 cases of traumatic hemorrhage into the ganglionic region (external capsule and lenticular nucleus) were included. They stated:

. . . . No example of gross hemorrhage into the posterior limb of the internal capsule, such as appears spontaneously in cases of hypertension or arteriosclerosis, has been observed by us. It may, therefore, be safely assumed that gross hemorrhage in this region is not the result of trauma, for, of all portions of the brain presenting evidences of injury, this particular region seems to be most notably free.

Jelsma<sup>2</sup> urged that traumatic hemorrhages be not "confused with apoplectiform lesions which are found in the internal capsule and deeper in the brain, though the traumatic clot may be as deeply placed as one in apoplexy." There have been numerous clinical descriptions of traumatic intracranial hemorrhage with involvement of internal capsule inferred by the existence of hemiparesis. Inasmuch as nearly all such cases represent recoveries after surgical evacuation of the clot or lack confirmation by autopsy, the evidence is indirect. Most such cases present the picture of *Spätapoplexie* of Bollinger with a time interval varying from days to months or even years. Only 1 instance of a traumatic fresh hemorrhage of the internal capsule at autopsy was found

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From the Department of Pathology, Queens General Hospital.

1. Courville, C. B., and Blomquist, O. A.: Traumatic Intracranial Hemorrhage, with Particular Reference to Its Pathogenesis and Its Relation to "Delayed Traumatic Apoplexy," Arch. Surg. 41:1 (July) 1940.

2. Jelsma, F.: Common Traumatic Lesions, Kentucky M. J. 34:264, 1936.

in the literature; this was described by Berner.<sup>3</sup> Several late effects of hemorrhage of the internal capsule ostensibly caused by trauma have been described, including an old lesion in the genu of the internal capsule eighteen years after the injury, described by Spiller.<sup>4</sup>

In this presentation we wish to offer 7 instances of verified traumatic hemorrhage of the internal capsule and to discuss the medicolegal significance of such lesions. Hemorrhage into the internal capsule occurring immediately at the time of injury is admittedly rare, having occurred in only 7 instances in approximately 320 cases of trauma of the head in which autopsy was done. The cases reported here all represent instances of established trauma with varying-sized hemorrhages in the internal capsule. In some, the hemorrhage was limited to the region of the internal capsule without other marked cerebral lesions and without fracture of the skull. In others extensive associated morphologic evidence of trauma was noted in the skull and in the brain. In all the internal capsule lesion bore no relation to any superficial brain laceration, contusion or source of bleeding. The hemorrhages truly represented independent deeply placed parenchymal foci of bleeding within the cerebrum. Hemorrhage into the adjacent basal ganglions was also present in several of them. All cases with hemorrhage into the basal ganglions as well as all other deeply placed hemorrhages without involvement of the internal capsule have been eliminated. The lesions described herein corresponded to the first type in the classification of traumatic hemorrhages by Bailey<sup>5</sup> and represented hemorrhages "which occur at the moment of injury."

#### REPORT OF CASES

CASE 1.—N. B., a 49 year old man, was found in coma at the foot of a subway stairway. A hematoma was noted over the left occipitoparietal area. Deep irregular breathing with bubbling rales and diminished reflexes were present. The spinal fluid was bloody. Death occurred within two hours. At autopsy multiple skull fractures were found in all fossae. Extensive contusion of the surface of the right frontal, parietal and temporal lobes was present, with adjacent petechial hemorrhages. On horizontal section, a hemorrhage 3 by 2 cm. was seen in the anterior limb of the left internal capsule (fig. 1 *A*), and a hemorrhage of similar size and shape was found beyond the genu at a deeper level in the posterior limb of the internal capsule (fig. 1 *B*). Smaller deeply placed petechial hemorrhages were noted in the head of the right caudate nucleus, the splenium of the corpus callosum, the pons and the floor of the fourth ventricle. The kidneys were natural, and the heart showed only limited hypertrophy. The clue to the cause of the fall in this instance was found in the recovery of 3 plus alcohol, equivalent to 15 cc. per hundred grams, from the brain and the liver. The alcoholism and the multiplicity and the severity of the traumatic lesions would tend to rule out coincidental spontaneous apoplexy.

3. Berner, O.: Pathological Anatomy of Traumatic Hemorrhages of Brain and Their Medicolegal Significance, *Norsk mag. f. lægevidensk.* **94**:1318, 1933.

4. Spiller, W. G.: Unilateral Traumatic Selective Degeneration of Pallidum and the Striatum, *Arch. Neurol. & Psychiat.* **35**:310 (Feb.) 1936.

5. Bailey, P.: Traumatic Apoplexy, *M. Rec.* **61**:528, 1904.

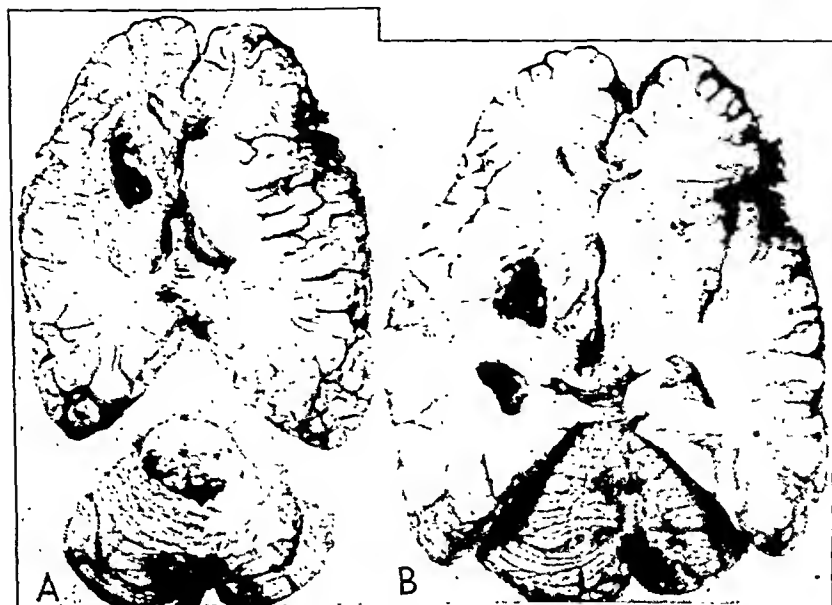


Fig. 1 (case 1).—*A*, section of the cerebrum and the brain stem showing hemorrhage in the anterior limb and the genu of the left internal capsule and the upper portion of the pons and the floor of the fourth ventricle. Note hemorrhage in the splenium of the corpus callosum. *B*, horizontal section of the cerebrum at the lower level showing hemorrhage in the posterior limb of the left internal capsule. Note surface laceration of the right frontal and temporal lobes.



Fig. 2 (case 2).—Section showing massive hemorrhage involving all but the most posterior portion of the right internal capsule, the lenticular nucleus and the adjacent subcortical white matter. Note distortion of the right lateral ventricle.



CASE 2.—G. C., a 31 year old man, was struck by a passing automobile while changing the tire on his car. He was brought to the hospital in coma and died shortly afterward. At autopsy external evidence of injury was found in the form of multiple abrasions and contusions of the face and the right and left frontal regions. Comminuted fracture of the nose was present, but careful examination of the skull revealed no other fracture. A small amount of subdural and subarachnoid hemorrhage was seen bilaterally. Horizontal section of the brain (fig. 2) showed a massive area of hemorrhage involving the right internal capsule, the lenticular nucleus and the regional gray and white matter extending as far laterally as the island of Reil. This area measured 4 by 7 cm. and extended to within 3 and 4 cm. of the surface cortex. No surface lacerations of the brain were found. A moderate amount of punctate hemorrhage was seen in the left frontal and right frontoparietal regions at the very junctions of gray and white matter.



Fig. 3 (case 3).—Section showing level above the main blood clot with multiple varying-sized discrete and confluent hemorrhages in the left internal capsule and the medial portion of the putamen.

CASE 3.—W. M., a 4 year old boy, fell from a ladder while playing with some friends and landed on his head. He died almost immediately. At autopsy extensive fractures of the vertex and the base of the skull were seen. There was separation of the frontoparietal suture on the right with a depressed fracture 1 by  $\frac{1}{2}$  in. (2.5 by 1.3 cm.) in the right frontoparietal region. On the left a linear fracture extended along the parietal bone. Both fractures were traced around to the base in the region of the sella turcica with complete separation of the anterior and posterior parts of the skull. Despite the extensive injury to the skull, the brain appeared normal externally. On horizontal section, an area of hemorrhage was observed in the left internal capsule which extended into the adjacent basal ganglions, particularly the lenticular nucleus. Figure 3 represents a photograph of the lesion at a level above the main blood clot. The area of

bleeding represented confluence of many small areas of hemorrhage. Although some petechiae were noted in the adjacent white matter, no other areas of hemorrhage were noted in the brain.

CASE 4.—N. J., an 8 year old boy, was struck by an automobile and died eight hours later without regaining consciousness. Abrasions but no lacerations were found about the face and the head. Autopsy revealed extensive basilar skull fracture with only limited surface lacerations in the frontal and right parietal regions. A horizontal section of the cerebrum revealed extensive focal hemorrhages in the white matter of the frontal lobes and the corpus callosum. There were numerous streaked hemorrhages throughout the entire length of the internal capsule on the left side, and a larger area of hemorrhage 1 cm. in diameter extended laterally from the internal capsule into the adjacent basal ganglia (fig. 4). A small hemorrhage was noted in the posterior limb of the right internal

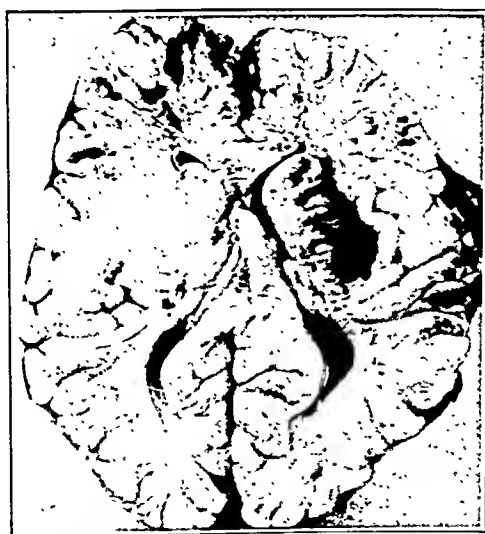


Fig. 4 (case 4).—Section showing multiple streaked hemorrhages in the left internal capsule and the adjacent putamen. Note extensive contusion and laceration of the left temporal and right frontal lobes. Note small hemorrhage in the posterior limb of the right internal capsule and numerous varying-sized concussion hemorrhages in subcortical white matter.

capsule. Dissection revealed no surface laceration or hemorrhage continuous with the lesion in the internal capsule.

CASE 5.—J. K., a 38 year old policeman, was thrown from his motorcycle while traveling at a considerable rate of speed. He was brought to the hospital in a comatose condition. He showed lacerations of both eyebrows with regional hematoma and ecchymosis of both orbits. Overactive knee jerks and bilateral ankle clonus were noted. He remained in coma, his temperature rising to 106 F. on the fourth hospital day with death occurring soon after. Autopsy revealed grouped focal hemorrhages involving the right internal capsule and the lenticular nucleus. Some of the hemorrhages measured more than 1 cm. in diameter and merged with adjacent hemorrhages of similar size. At a deeper level isolated

smaller focal hemorrhages were found in both anterior and posterior limbs of the internal capsule. A few streaked hemorrhages were seen in the subcortical white matter in the region of the frontal and parietal lobes on the same side. No skull fracture was present.

CASE 6.—P. D., a 45 year old white woman, was injured in an automobile accident and was brought to the hospital in an unconscious state and in shock. There was laceration of the chin and contusion of the face just above the forehead; large laceration of the scalp was also present. There were comminuted fractures of the tibia and the fibula. The left pupil was larger than the right, and both reacted. She improved for a few hours and then became restless, went into deep coma and died two days later. At autopsy the brain revealed grouped



Fig. 5 (case 6).—Section showing grouped small hemorrhages in the posterior limb and the genu of the right internal capsule. Some of the blood clot has been displaced.

small focal areas of hemorrhage in the region of the genu extending backward for approximately half of the posterior limb of the right internal capsule (fig. 5). A smaller zone of softening or hemorrhage was noted in the corresponding area of the other internal capsule. A single small hemorrhage was also found in the left lateral wall of the fourth ventricle. No skull fracture was seen, and no bleeding into the ventricular system or in relation to the cerebral meninges was found. The immediate cause of death was extensive bronchopneumonia.

CASE 7.—J. B., a 28 year old jockey, was thrown from his horse during a race, became unconscious immediately and showed laceration of the right side of the head with hematoma of the temple. He was incontinent, and decerebrate spasm developed. The jaws were fixed. Reflexes on the right were hyper-

active, but the right arm and leg were flaccid. The left arm and leg were spastic. Abdominal reflexes were absent. A right-sided ankle clonus was present, and the knee jerk was hyperactive on the right. Bilateral Babinski reflexes were noted. Roentgen examination of the skull failed to reveal any fracture. The frequency of the decerebrate spells lessened for a while, but the right-sided paresis persisted. The right pupil was three times larger than the left and failed to react to light. The spinal fluid was bloody. Hyperpyrexial signs of pneumonia developed, and death occurred six days after admission. Clinical diagnosis by Dr. Richard Grimes was contusion and laceration of the left temporal lobe and traumatic left intracerebral hemorrhage. At autopsy extensive hemorrhage was found low down in the posterior limb of the internal capsule just above the cerebral peduncle on the left side extending into the lateral portion of the adjacent thalamus. Some small areas of hemorrhage were noted elsewhere in the basal ganglions in the thalamus in the internal capsule, in the cerebrum and in the cerebellum. No skull fracture was found.



Fig. 6 (case 7).—Coronal section of the inferior portion of the cerebral hemisphere showing large area of hemorrhage in the posterior limb of the internal capsule just above the cerebral peduncle on the left side. Note involvement of the lateral portion of the thalamus and the subcortical white matter.

#### COMMENT

The differentiation of spontaneous intracerebral hemorrhage from the variety of intracerebral hemorrhage due to trauma ordinarily presents no difficulty. The so-called spontaneous medical hemorrhage, or apoplexy, is centrally placed in the cerebrum with evidence of external trauma in the form of injury to the scalp, the skull and the surface of the brain, ordinarily only minimal. The history usually rules out any causative trauma and establishes the sequence of events. Spontaneous hemorrhage is naturally associated with local vascular disease. It is more common in the older age group and often occurs under circumstances under which contributory trauma is impossible. Generalized vascular disease, hypertension, local atheroma, sclerosis and syphilis often will be found in the spontaneous variety of hemorrhage.

There are no trustworthy gross pathognomonic features of spontaneous hemorrhage to differentiate it from the traumatic variety. The adjacent tissue does usually show more widespread distribution of small petechiae in the nontraumatic lesions. The zone of softening is also usually wider. There is usually a gradation in size and number of the petechiae about the zone of spontaneous hemorrhage. There exists a greater tendency to respect and preserve the natural landmarks of the brain, no doubt dependent on the individuality of blood supply. Multiple foci of bleeding are less common in apoplexy. We have seen, however, numerous instances of blowout hemorrhages in the pons when a spontaneous hemorrhage extended into the ventricular system without any associated trauma. In general spontaneous hemorrhage is placed in the region of the geometric center of the corresponding mass of brain tissue. In the cerebrum this does correspond approximately to the region of the internal capsule and adjacent basal ganglions, and the lenticulostriate vessels are usually implicated as the main source in this location.

In contrast traumatic intracerebral hemorrhages are usually associated with considerable evidence of external trauma in the form of contusion and laceration of the brain surface or by scalp and/or skull injury. In 4 of the cases in the group presented here there was extensive injury. It is of pointed interest, however, to call attention to the fact that no fracture of the vault or the base was present in 4 of the 7 cases. Evidence of injury to the surface of the cerebral cortex was entirely lacking in case 3 even though an extensive fracture of the skull was present. The age incidence in the present group of traumatic hemorrhages is impressive. Four patients were under 40 with 1 child 4 years old and another 8 years of age. The youth of these patients rules out consideration of basic vascular disease, such as is found in older persons. All circumstances favor dissociation from vascular disease. Subdural or epidural hemorrhages are common following trauma, but subarachnoid hemorrhages may be associated with both trauma and nontraumatic lesions. In general hemorrhages due to trauma tend to be multiple and are placed in the external aspect of the brain. We do not agree with Bailey that in all cases of traumatic intracerebral hemorrhages some previous disease process exists in the vessels. The cerebral vessels will more often be found normal in cases of traumatic hemorrhages, whether superficial or deep.

There are two types of traumatic intracerebral hemorrhage. One form is superficially placed and represents a gyrus distended by blood clot. This usually results from venous bleeding. This blood clot takes an interval of time to appear, and it is this form of intracerebral hemorrhage which constitutes the more common basis for *Spätapoplexie*. This particular form of traumatic hemorrhage is of considerable clinical

importance and has received a great deal of surgical study recently. This expanding blood clot may be looked on as a variant of the ordinary subdural hemorrhage, and the clinical pictures approach each other. Such traumatic hemorrhages are found usually in the region of a surface contusion and laceration. This form of hemorrhage can reach considerable size and act like any expanding lesion. Numerous instances of identification by clinical means, with and without the aid of encephalography, with subsequent recovery for the patient are found in the literature. They all have in common the feature of extending to the surface of the brain usually at the focus of origin.

Another form of traumatic hemorrhage is the so-called concussion or blowout hemorrhage with no connection with any surface lesion of the brain. This form particularly comes well within the scope of our present study. The pons is the favorite site for such lesions. These may be found throughout the brain. They are seen more often in the white matter of the cerebrum and in the gray matter of the spinal cord. In the pons they have a characteristic streaked appearance, undoubtedly caused by the orientation of fiber tracts. A similar streaked appearance is noted in the region of the internal capsule in figure 4. Other than their location in the pons there seems to exist no particular preferential site.

Courville and Blomquist have analyzed the relation of the direction of force in injury to the location of the hemorrhages within the brain. They favor the impact of the force in the temporal region for deeply placed ganglionic hemorrhages. In only 1 of our cases was there external evidence of trauma in the lateral temporal region. In 4 of the cases the force of injury was apparently applied to the region of the face. In the other 2 there was scalp injury in the region of the vertex or the occipitoparietal areas. We have seen a wide range of gradation in size and form of such traumatic concussion or blowout hemorrhages. They vary in different cases of trauma and in the same case. Microscopic hemorrhages and petechiae may be associated with larger varying-sized blood clots. The multiplicity of such lesions helps establish their traumatic nature readily. When, however, a single large concussion or blowout hemorrhage is found centrally placed, particularly in the internal capsule, and the history of trauma is equivocal in an older person with hypertension, the lesion may readily be interpreted as spontaneous apoplexy. It follows that any evidence of trauma present will be misinterpreted as secondary and as precipitated by the hemorrhage.

The following case of spontaneous bleeding represents a single instance that is chosen because of the excellence of contrast to case 1 in the series already presented. From the standpoint of circumstantial evidence, both persons were found at the bottom of a stairway in coma. Both showed hemorrhage into the internal capsule, yet the lesion of one

was traumatic in origin (case 1), the person having fallen because of his inebriation; and the other was obviously spontaneous (case 8) with the fall and the injury precipitated by spontaneous hemorrhage in the internal capsule caused by underlying vascular disease.

CASE 8.—An 82 year old man was admitted in coma, having been found at the foot of the cellar steps. He showed a hematoma in the left temporal region. The pupils were pinpoint and fixed. Spinal tap showed no increase in pressure. There were 100 cells per cubic millimeter with lymphocytes predominating and only a few red blood cells. Generalized convulsions appeared, and the patient required amytal. Muscle rigidity was absent on admission but appeared on the third day. The temperature rose to 102.4 F. with the pulse becoming imperceptible and respiration ceasing shortly after. There was no return of consciousness during the entire stay in the hospital. At autopsy the brain showed a deeply



Fig. 7 (case 8).—Section showing massive spontaneous hemorrhage into the posterior limb of the internal capsule with involvement of the regional white matter of the parietal and occipital lobes. Note blood clot in ventricle.

placed massive left internal capsular hemorrhage with involvement of the optic radiation and regional white matter of the parietal lobe. Extension to the ventricular system was present. Some surface lesions were found in the left frontoparietal region but were of a limited nature. The kidney showed rather severe nephrosclerosis, and the heart showed marked hypertrophy with prominent involvement of the left ventricle.

In none of the cases in which there was a history of trauma was there evident disease of the cerebral vessels. The initial hemorrhage was undoubtedly due to the direct trauma. The presentation of the 7 cases of traumatic hemorrhage into the internal capsule should call attention to the possibility that lesions in this region, ordinarily accepted as the focus for spontaneous hemorrhage only, may occur as the result

of trauma. In the present day, when trauma plays such an important role in our routine lives, this realization is of importance to avoid occasional dislocation of justice. In all the cases represented hemorrhage with trauma was the obvious mechanism, yet the findings simulated those of spontaneous apoplexy. Variations from petechiae to bulky blood clots are represented. It should be stressed that such hemorrhages may occur with and without the skull fracture. Courville and Blomquist have discussed the location of this form of hemorrhage throughout the brain and in the basal ganglions limited to the lenticular nucleus and the external capsule. No group of cases of traumatic hemorrhages localized in the internal capsule at autopsy has been found in the literature.

Discussion of the mechanism involved in the concept of such blowout hemorrhages is being reserved for a future presentation, with the inclusion of some experimental data. The causation of concussion or blowout hemorrhages, of which the cases presented are merely larger variants, has been studied by numerous authors.<sup>6</sup> Let it suffice here to state that concussion or blowout hemorrhages are identical in the internal capsule, whether small or large, with the ordinary concussion or blowout hemorrhages seen so often in the pons or elsewhere in the white matter in cases of trauma of the brain. We do not wish to enter into the controversy as to the relation of such focal and petechial hemorrhages to the syndrome of concussion. We merely wish to imply that in some cases of head trauma such multiple focal hemorrhages occur. This does not deny the existence of the syndrome of concussion without the existence of such hemorrhagic lesions. For this purpose the descriptive term blowout hemorrhages is distinctly preferable.

Whether smaller focal areas of hemorrhage of this sort might be the site of subsequent spontaneous apoplexy is an open question. The accepted propensity of massive hemorrhage to occur in focal areas of

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old softening or hemorrhage does give significance to traumatic lesions of the internal capsule too small to contribute to the symptom picture at the time of injury. A theoretic basis is thus offered for the delayed contribution by trauma to the causation of a second and much rarer form of *Spätapoplexie*. Injuries without immediate major evidence of bleeding into the internal capsule thus can be of some importance. It must be emphasized that although this form of *Spätapoplexie* seems to be frequently discussed in the literature it is distinctly rare in our own experience. It is as yet based on little demonstrative evidence and lacks full confirmation.

#### CONCLUSIONS

Traumatic hemorrhages of considerable size can involve the internal capsule. Seven cases are presented.

Such hemorrhages may be confused with spontaneous cerebral hemorrhage on the basis of their location.

The history, circumstances of injury, analysis of associated brain and skull trauma and basic vascular and other lesions established by a complete autopsy procedure are essential for the proper analysis and understanding of hemorrhages occurring in this location as elsewhere in the brain surface.

It is suggested that such hemorrhages are variations of the ordinary concussion or blowout hemorrhages with an identical causal mechanism.

Dr. Richard Grimes, Assistant Medical Examiner, allowed us to study much of the material used in this paper.

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# TOTAL CIRCULATING PLASMA PROTEINS IN SURGICAL PATIENTS WITH DEHYDRATION AND MALNUTRITION

INDICATIONS FOR INTRAVENOUS ALIMENTATION WITH  
AMINO ACIDS

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AND

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In recent years a great deal of emphasis has been placed on the preoperative and the postoperative care of surgical patients<sup>1</sup> with the hope of further reducing the mortality rate. With such a major surgical procedure as gastric resection, pulmonary complications (atelectasis, pulmonary edema and bronchopneumonia) play an important role. With the improvements in operative technic and anesthesia these conditions now account for a large percentage of the postoperative complications that still exist. With the advent of the use of sulfonamide compounds the mortality rate will probably be further reduced, but it has always been the hope that pulmonary complications could be prevented and that the added risk to the patient and the need for treatment could therefore be eliminated.

The removal of mucus by intratracheal aspiration,<sup>2</sup> hyperventilation of the lungs<sup>3</sup> and careful application of adhesive tape and abdominal binders<sup>4</sup> to prevent restriction of the thoracic cage have all contributed to more efficient postoperative care. It is believed, moreover, that by employment of gastric suction ileus may be avoided and thus the diaphragm will have more freedom of motion and aerate the lungs more

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This study was aided by a grant from the John and Mary R. Markle Foundation.

From the Departments of Surgery and Biochemistry, Western Reserve University School of Medicine.

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efficiently. Furthermore, it has been stated that the type of anesthesia employed (inhalation, spinal or local) apparently does not alter the incidence of pulmonary complications appreciably but that the duration of the anesthesia is of considerable importance.<sup>5</sup>

Nutritional disorders have been carefully studied, and it has been generally accepted that pulmonary complications occur more frequently in elderly malnourished patients than in others.<sup>6</sup> At the University Hospitals of Cleveland it was found that the mortality rate associated with gastric resection fairly well paralleled the magnitude of the loss of weight in patients with chronic peptic ulcer.<sup>7</sup> It was noted also that patients who showed moderate anemia on admission to the hospital and were given 1,000 to 2,000 cc. of whole blood prior to operation often did much better than patients who had normal blood values on admission and did not receive transfusions because it was assumed that they were not necessary. Hence, this has led us to believe that often a decrease in the plasma volume associated with chronic dehydration masks anemia and hypoproteinemia. In further support of this it was observed that in many instances patients who were admitted because of a gastric lesion had hematocrit values and protein concentrations near normal on admission but had profound drops in these levels after operation without evidence of bleeding, apparently due to hemodilution.

In a recent publication by Walters, Gray and Priestley<sup>6</sup> on carcinoma of the stomach it was stated that malnutrition may be severe and a negative nitrogen balance may exist in such cases but that the depletion of the plasma protein does not often reach levels which are clinically important. Furthermore, it was stated that the degree of anemia more or less indicates the duration of the tumor.

This study was undertaken to demonstrate in an unselected group of patients with carcinoma of the gastrointestinal tract or pyloric stenosis due to ulcer (1) that a protein-deficient state may exist and the plasma protein concentration may be an unreliable index of the extent of the deficiency and (2) that in addition to acute dehydration (primarily due to vomiting) chronic dehydration (principally due to a prolonged inadequate fluid intake) may occur and that the hematocrit value, the plasma protein concentration, the hemoglobin content and the plasma chloride level may not be of value in estimating the magnitude of this prolonged loss of body water.

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## METHODS

The plasma volume was measured by the Evans' blue dye (T-1824)<sup>8</sup> method as described by Gregersen and Stewart<sup>9</sup> and modified by Gibson and Evelyn<sup>10</sup> for the photoelectric colorimeter. The expected normal plasma volume was calculated from the body surface area,<sup>11</sup> and it may be stated that since these patients had lost from 10 to 50 pounds (4.5 to 22.7 Kg.) of weight such estimated values would err on the side of being too low.<sup>12</sup> The hematocrit value was determined in duplicate on heparinized blood without dilution by employing Van Allen cell volume tubes,<sup>13</sup> and the plasma protein concentration was for the most part obtained by the micro-Kjeldahl technic. Occasionally the falling drop method as described by Barbour and Hamilton<sup>14</sup> was employed. The value for total circulating plasma proteins was calculated by multiplying the plasma volume in cubic centimeters by the protein concentration per cubic centimeter. A plasma protein concentration of 7 Gm. per hundred cubic centimeters was considered as an arbitrary normal value, and by multiplying that figure by the expected plasma volume and dividing by 100, the expected normal value for total circulating plasma proteins was determined.

## RESULTS

The findings are recorded in table 1. In each instance (except for patients 4 and 9) there was a diminished plasma volume. Patients 4 and 9 had moderate anemia on admission to the hospital and received between 1,200 and 2,200 cc. of blood prior to the time our studies were performed. Both of these patients underwent strenuous surgical procedures and had uneventful convalescences.

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8. Supplied by the Warner Institute for Therapeutic Research, New York.

9. Gregersen, M. I., and Stewart, J. D.: Simultaneous Determinations of Plasma Volume with T-1824 and "Available Fluid" Volume with Sodium Thiocyanate, *Am. J. Physiol.* **125**:142-152, 1939.

10. Gibson, J. G., and Evelyn, K.: Clinical Studies of the Blood Volume: IV. Adaptation of the Methods to the Photoelectric Microcolorimeter, *J. Clin. Investigation* **17**:153-158, 1938.

11. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of Blood Volume: Clinical Application of Method Employing Azo Dye "Evans Blue" and Spectrophotometer, *J. Clin. Investigation* **16**:301-316, 1937.

12. For example, the expected normal plasma volume for patient 8 (table 1), calculated on the basis of weight (57 Kg.) and height (166 cm.) at the time of the study, was 2,600 cc. Prior to his illness the patient weighed 75 Kg., and with the height unchanged the estimated plasma volume was 2,950 cc. Thus the observed plasma volume (2,140 cc.) would be 73 per cent rather than 82 per cent of normal. In addition, the expected normal value for total circulating plasma proteins would be 206 instead of 183 Gm.

13. Van Allen, C. M.: An Hematocrit Method, abstracted, *J. A. M. A.* **84**: 202-203 (Jan. 17) 1925.

14. Barbour, H. G., and Hamilton, W. F.: The Falling Drop Method for Determining Specific Gravity: Clinical Applications, *J. A. M. A.* **88**:91-94 (Jan. 8) 1927.

Patient 1 was a man who appeared in moderately good condition on admission to the hospital but gave a history of a loss of 20 pounds (9 Kg.) in weight, occasional episodes of nausea and vomiting and anorexia for three and one-half months. His plasma chloride level was 102 milliequivalents per liter at the time our studies were done. His plasma volume was 66 per cent of his expected normal volume, and although the protein concentration (6.40 Gm. per hundred cubic centimeters) appeared to be near the normal range, the value for total

TABLE 1.—*Values for Plasma Volume and Total Circulating Plasma Proteins of Surgical Patients with Malnutrition*

Patient	Diagnosis	Measured Plasma Volume, Cc.	Expected Plasma Volume, Cc.*	Plasma Volume, Percentage of Normal	Hematocrit Value	Plasma Protein Concentration, Gm. per 100 Cc.	Plasma Protein Concentration, Percentage of Normal	Total Circulating Plasma Proteins, Gm.	Expected Total Circulating Plasma Proteins, Gm.	Total Circulating Plasma Protein, Percentage of Normal
1	Carcinoma of stomach.....	1,640	2,500	66	47	6.40	91	105	175	60
2	Carcinoma of stomach.....	1,990	2,690	74	38	5.85	84	110	183	62
3	Carcinoma of stomach with extension to esophagus.....	1,870	2,900	64	41	5.46	78	102	203	50
4	Carcinoma of stomach.....	2,900	2,950	98	44	6.05	95	193	206	94
5	Carcinoma of stomach.....	2,100	2,710	77	44	6.40	92	136	190	72
6	Pyloric stenosis due to ulcer.....	1,480	2,040	73	37	6.15	83	91	143	64
7	Pyloric stenosis due to ulcer.....	2,600	2,760	94	40	5.44	78	142	193	73
8	Pyloric stenosis due to ulcer.....	2,140	2,600	82	40	5.92	85	127	183	69
9	Carcinoma of sigmoid flexure with obstruction.....	2,030	2,370	86	37	6.22	89	127	166	77
10	Carcinoma of transverse colon...	3,700	3,040	122	42	7.46	107	276	213	129
11	Malnutrition; hemorrhage into large ovarian cyst.....	2,490	2,780	90	42	6.48	93	161	195	83
12	Carcinoma of pancreas; malnutrition; edema.....	2,330	2,770	84	33	5.06	72	118	194	61
13	Malnutrition; edema.....	2,660	2,830	94	42	5.30	76	141	198	71
14	Carcinoma of stomach.....	2,350	2,460	95	43	6.03	86	142	172	83

\* Calculated from body surface area.

circulating proteins was 60 per cent of the expected normal. It is likely that most of the dehydration was a result of a prolonged diminished intake rather than of an extensive loss of fluids by vomiting. If it is assumed that the observed plasma volume could be restored to the expected volume by the addition of physiologic solution of sodium chloride and the total circulating proteins remain at 105 Gm., the protein concentration would then fall to 4.20 Gm. (105.0/25). A comparable situation apparently occurred in patients 6 and 7 postoperatively, largely because of the injudicious use of physiologic solution of sodium chloride. In patient 6 by the fourth postoperative day the plasma protein concentration was 4.64 Gm. per hundred cubic centimeters, and generalized

edema was present. The intake of sodium chloride was restricted, and mercurpurin and two transfusions of plasma were given. The edema disappeared, and the protein concentration returned to a normal level. This patient had a plasma chloride level of 89 milliequivalents per liter shortly after admission to the hospital. While physiologic solution of sodium chloride was indicated for the hydration of this patient and the plasma protein concentration (6.15 Gm. per hundred cubic centimeters) was well above the so-called edema level, a restoration of the plasma volume to the expected normal in the presence of an amount of total circulating proteins 64 per cent of normal would result in a precipitous fall in the plasma protein concentration to 4.45 Gm. per hundred cubic centimeters ( $91 \times 100/2,040$ ).

Patient 7 was moderately dehydrated on admission to the hospital, largely because of inadequate intake of food and water and occasional vomiting. At this time the hematocrit value was 46 and the plasma protein concentration 6.95 Gm. per hundred cubic centimeters. The patient was given 3,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride intravenously for three days, and our studies were then made the night prior to operation. The plasma volume had apparently been restored to near normal by the administration of water and electrolytes, but at the same time the hematocrit value and the plasma protein concentration were lower because of dilution. The patient was operated on the next day and given 400 cc. of plasma and 3,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride. On the morning of the first postoperative day he was given 2,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride. By noon he had a plasma protein concentration of 5 Gm. per hundred cubic centimeters. Fairly profuse pulmonary edema also had developed, and later atelectasis and bronchopneumonia. At this time it was thought advisable to give a transfusion of blood or plasma and to discontinue the administration of physiologic solution of sodium chloride until the protein level was restored. The patient eventually recovered, but it seems likely that the pulmonary complications might have been avoided. Studies were repeated one month after the operation. At this time the plasma volume had risen to 2,920 cc. and the protein concentration to 6.78 Gm. per hundred cubic centimeters. The amount of total circulating plasma proteins (198 Gm.) compared favorably with the expected normal, which had been calculated prior to the operation.

Patient 8 had total circulating proteins similar in per cent of normal to those of patient 7. This patient was given more plasma and whole blood than the preceding patient, and physiologic solution of sodium chloride was restricted to 900 to 1,000 cc. daily during the immediate postoperative period. The temperature showed only a slight elevation and then returned to normal while the patient was going through an entirely uncomplicated convalescence.

Patient 12 is of interest from the standpoint of therapy. He was a 60 year old man admitted to the hospital because of jaundice. At operation he was found to have carcinoma of the head of the pancreas, and therefore cholecystogastrostomy was performed. Postoperatively his convalescence was complicated by pneumonia and disruption of the wound. He had lost 15 pounds (7 Kg.) prior to his admission to the hospital and because of the prolonged convalescence had continued to lose weight. The patient was seen by us approximately two months after the operation, and studies of plasma volume were made (table 1). At this time he had generalized nutritional edema which had failed to respond to diuretics and transfusions of plasma. He took in a meager diet orally and was in negative nitrogen balance (5 to 8 Gm. daily). Since this patient was metabolizing 40 to 60 Gm. of his own body proteins daily, it was thought that he should have an intake of 60 to 75 Gm. of protein a day plus adequate calories. He was therefore given intravenously 15 per cent amino acids<sup>15</sup> mixed with 10 per cent dextrose. In three days he was free of edema, although his plasma protein concentration had fallen to 4.70 Gm. per hundred cubic centimeters, apparently owing to dilution. The patient was given 60 Gm. of amino acids and 200 to 300 Gm. of dextrose intravenously for ten of the next twelve days.

During this time his entire caloric intake was derived solely from intravenous therapy and he was maintained in positive nitrogen balance. At the end of this time studies of plasma volume were repeated and showed an increase of 600 cc. The protein concentration was 5.10 Gm. By comparison with the original level of 5.06 Gm. this seemed to indicate no improvement, but actually the total circulating proteins increased by 26 per cent (31 Gm.) owing to the increased plasma volume. The patient's appetite greatly improved, and he was able to maintain his caloric intake orally until the time of discharge from the hospital, two weeks later. The protein concentration at this time was above 6 Gm. per hundred cubic centimeters.

Patient 13 was a psychiatric patient who had been admitted to the hospital largely for study. While he was in the hospital, it was found that he had benign prostatic hypertrophy with urinary retention. Urethral drainage was instituted, and shortly thereafter pneumonia developed. Because of the complications the patient's caloric intake had been inadequate, and marked nutritional edema developed. He showed a daily urinary output of nitrogen of 7 to 9 Gm. with an intake of only 2 or 3 Gm. He was given no further feedings for twelve days and was maintained in slightly positive nitrogen balance by intravenous administration of amino acids and dextrose. The protein concentration

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15. Fifteen per cent amino acids supplied by Frederick Stearns & Co., Detroit.

rose from 5.30 to 6.43 Gm. per hundred cubic centimeters, and although this seemed to indicate a rather pronounced increase (by comparison with the concentration in the preceding patient), his plasma volume showed a slight decrease. Thus the total circulating proteins had increased by 20 per cent. In this patient, as in the preceding one, diuresis occurred shortly after the amino acids and 10 per cent dextrose were given. At the time therapy was discontinued, the patient was free of edema and able to take an adequate oral diet. It has been thought that the diuretic action was obtained largely from the conversion of amino acids into urea (80 to 90 per cent of the total nitrogen in the urine in these cases is made up of urea nitrogen). Little information could be

TABLE 2.—*Fluid Management in a Case of Bleeding Peptic Ulcer*

Date	Parenteral Intake, Cc.		Oral Intake	Total Output	Hematocrit Value	Plasma Protein Concentration, Gm. per 100 Cc.
	Intravenous	Subcutaneous *				
10/28.....	930	.....	1,070	1,200	..	4.52
10/29: 1 p. m.....	.....	.....	460	600	19	4.10
10 p. m. (operation)...	2,000 (blood)	.....	.....	.....	17	3.88
10/30: 2 a. m.....	2,450 (blood)	.....	.....	.....	33	5.44
9 a. m.....	450 (5% dextrose)	.....	.....	2,235	32	5.20
5 p. m.....	.....	.....	.....	.....	34	5.31
10/31.....	350 (plasma)	2,630	.....	550	33	5.52
11/ 1.....	1,000 (5% dextrose)	3,000	.....	1,200	39	6.80
11/ 2.....	2,000	.....	90	2,400	..	....
11/ 3.....	.....	1,500	550	1,300	30	5.72
11/14.....	.....	.....	2,300	900	37	5.73

\* Five per cent dextrose in physiologic solution of sodium chloride.

gained as to the efficacy of parenteral amino acid therapy by following only the plasma protein concentration. As has been demonstrated in the case of patient 12, a 26 per cent increase occurred in the total circulating plasma protein level when the plasma protein concentration remained the same and the hematocrit value showed a slight increase. An accurate evaluation of such therapy could be obtained only by making studies of nitrogen balance and determinations of plasma volume. Patients 5 and 6 in this series were also treated with intravenous injections of amino acids, and positive nitrogen balance was maintained, but the treatment was continued only until a 12 per cent increase in the total circulating proteins was obtained.

It has also been observed at this hospital that the mortality rate associated with surgical intervention in cases in which medical treatment



of an active bleeding ulcer was unsuccessful is high. Pulmonary complications in two to five days account for most of the deaths. Here again it was found that many of these patients were receiving only 700 to 1,000 cc. of blood at the time of operation and then large quantities of physiologic solution of sodium chloride. The plasma protein concentrations were uniformly low. In table 2 the results are shown for a 55 year old patient who had repeated gastric hemorrhages. The hematocrit value was 17; the plasma protein concentration was 3.98 Gm. per hundred cubic centimeters, and the systolic blood pressure was 50 when gastric resection was undertaken. The patient was given 4,450 cc. of blood and 350 cc. of plasma during the first forty-eight hours postoperatively and 1,800 cc. of physiologic solution of sodium chloride and 1,250 cc. of 5 per cent dextrose. His convalescence was entirely uneventful, and he was discharged fifteen days after operation.

#### COMMENT

From the cases presented in table 1 it can be seen that in patients who have shown a moderate loss of weight and a diminished intake of food and fluid severe dehydration may exist even though vomiting has not occurred or has been minimal. Also evidence has been given that normal hematocrit values (red blood cell counts and hemoglobin concentrations) and plasma protein concentrations may be obtained when dehydration is accompanied by malnutrition.

It should be kept in mind that patients who have diminished total circulating plasma proteins are likely to have in addition a deficit in tissue proteins in the liver and other organs. This is in keeping with the fact that a negative nitrogen balance exists. Any replacement therapy should be employed, therefore, with the purpose of restoring the entire protein deficit of the body and supplying adequate calories so that the body will no longer derive energy from the breakdown of its own tissues.

In recent years much has appeared in the literature concerning the role of hypoproteinemia in patients with wound dehiscence.<sup>16</sup> Since protein synthesis occurs at the site of a healing wound and the amino acids are the structural units of tissue proteins, it is reasonable to believe that the availability of the needed amino acids is of primary importance. Thus it would appear more logical to associate wound disruption with the presence and the extent of negative nitrogen balance (catabolism of body proteins) rather than solely with the concentration of plasma

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16. Whipple, A. O.: Address of President: Critical Latent or Lag Period in Healing of Wounds, *Ann. Surg.* **112**:481-488, 1940. Hartzell, J. B.; Winfield, J. M., and Irvin, J. L.: Plasma Vitamin C and Serum Protein Levels in Wound Disruption, *J. A. M. A.* **116**:669-674 (Feb. 22) 1941.

protein. For example, the wound of patient 12 disrupted when the concentration of protein was above 6 Gm. per hundred cubic centimeters and the catabolic process was probably at its maximum. Later several persistent decubiti healed rapidly and a severe lesion of the mouth healed when the plasma protein concentration was around 5 Gm. per hundred cubic centimeters and the body was receiving adequate calories and proteins so that a relatively normal anabolic process existed. This rapid healing has also been noted in treating similar patients by repeated transfusions of plasma.

Patients with malnutrition should receive from 50 to 80 Gm. of nutritionally adequate protein daily and sufficient total calories to protect this. It is naturally important that when fluids must be administered parenterally dextrose be given in adequate amounts so that proteins will not be metabolized solely for body energy but rather be spared so that the constituent amino acids may enter into the synthesis of other tissue proteins. Since it is impractical to administer 1,000 cc. of plasma daily (containing approximately 70 Gm. of protein), a preparation containing amino acids more or less in the proportion in which they occur in a biologically complete protein (for example hydrolysate of casein) would seem to be a likely substitute. At the University Hospitals of Cleveland such a product has been employed without any apparent ill effects. Patients have been maintained in positive nitrogen balance when their sole source of nitrogen has been 15 per cent amino acids given intravenously. The only difficulty encountered has been in supplying adequate amounts of dextrose along with the amino acids. Such a procedure is not difficult for two or three days, but when 10 per cent dextrose is employed to increase the caloric intake thrombosis of veins frequently occurs after twenty-four to seventy-two hours. Intrasternal injections as employed by Tocantins<sup>17</sup> might offer a solution to this problem.<sup>17a</sup> Naturally oral feedings or orojejunal tube<sup>18</sup> feedings would be the most physiologic and desirable method, but these were possible for only a few of the patients presented. Furthermore, supplementary intravenous therapy is frequently advantageous for patients with restricted oral feedings.

Certain rules,<sup>19</sup> employing the plasma chloride concentration, have been advocated to guide the clinician in treating patients who are

17. Tocantins, L. M., and O'Neill, J. F.: Infusion of Blood and Other Fluids into the Circulation Via the Bone Marrow: Technic and Results, *Surg., Gynec. & Obst.* 73:281-287, 1941.

17a. Since acceptance of this paper intrasternal administration of amino acids has been carried out on 1 patient with satisfactory results.

18. Stengel, A., Jr., and Ravdin, I. S.: The Maintenance of Nutrition in Surgical Patients with a Description of the Orojejunal Method of Feeding, *Surgery* 6:511-519, 1939.

19. Coller, F. A., and Maddock, W. G.: Water and Electrolyte Balance, *Surg., Gynec. & Obst.* 70:340-354, 1940.

dehydrated. Such methods would naturally be of great advantage if practical; often however, they give the physician a false sense of security. For example, a low plasma chloride level may occur with dehydration, but it alone gives one no idea as to how much physiologic solution of sodium chloride can be safely administered. As already pointed out, the total circulating plasma proteins would be the only index of the amount which could be safely tolerated. Coller and Maddock<sup>19</sup> pointed out that the thoughtless use of physiologic solution of sodium chloride is definitely harmful, especially to the sick surgical patient. From experimental work on animals<sup>20</sup> and from clinical observations, it is believed that a state of dehydration may frequently occur which is not quantitatively demonstrable by the plasma chloride level, the hematocrit value or the plasma protein concentration. On the other hand, it is known also that if the fluid lost has the same electrolyte pattern (quantitatively and osmotically) as plasma the concentrations of sodium and chloride in the plasma may be normal when the body is in great need of physiologic solution of sodium chloride.

As McIver and Gamble<sup>21</sup> stated in 1928:

. . . Hepatic duct bile and fluid derived from the intestinal mucosa contain approximately the same amount of fixed base and chloride ion as does plasma. Loss of this fluid will cause a reduction of the volume of the blood plasma and of interstitial fluid but should not alter the plasma chloride (or bicarbonate) concentrations.

Thus they concluded that:

. . . A point of great practical importance to be derived from this is that it is entirely incorrect to regard the plasma chloride concentration as an index of the degree of dehydration and of the extent to which replacement by salt solution is required.

Gamble and Ross<sup>22</sup> in 1925 brought out the fact that the loss of sodium rather than of the chloride ion is the significant factor in determining the extent of dehydration, since quantitatively sodium is the chief cation of the extracellular fluid and since the loss of chloride ion is compensated for by a corresponding increase in bicarbonate.

Data<sup>20b</sup> from our laboratory showed that animals which were not given food and water by mouth for three to seven days showed plasma

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20. (a) Mellors, R. C.; Muntwyler, E.; Mautz, F. R., and Abbott, W. E.: Changes of the Plasma Volume and "Available (Thiocyanate) Fluid" in Experimental Dehydration, *J. Biol. Chem.* **144**:785-793 (Aug.) 1942. (b) Abbott, W. E.; Mellors, R. C., and Muntwyler, E.: Fluid, Protein and Electrolyte Alterations in Experimental Intestinal Obstruction, *Ann. Surg.* **117**:39-51 (Jan.) 1943.

21. McIver, M. A., and Gamble, J. L.: Body Fluid Changes Due to Upper Intestinal Obstruction, *J. A. M. A.* **91**:1589-1592 (Nov. 24) 1928.

22. Gamble, J. L., and Ross, S. G.: The Factors in Dehydration Following Pyloric Obstruction, *J. Clin. Investigation* **1**:403-421, 1925.

volumes decreased by 15 to 30 per cent and still had plasma chloride levels of 110 to 120 milliequivalents per liter.

The hematocrit values and the protein concentrations in certain cases may be within the normal range when the total circulating red blood cells or the total amount of plasma protein is greatly decreased (table 1). It has been pointed out by Scudder<sup>23</sup> that the hematocrit value might be confusing in cases of dehydration because of anemia, but little has been said about the total circulating amount of plasma protein or the protein concentration. In 1927, however, Peters<sup>24</sup> did state that conditions that cause malnutrition frequently lead also to dehydration, and the latter by producing hemoconcentration may mask the reduction in the plasma protein level. In this article he also stated that the plasma protein concentration of a patient with carcinoma of the stomach fell from 5.87 to 4.69 Gm. per hundred cubic centimeters after the administration of a solution of sodium chloride. Because of the chronic course of patients with carcinoma of the stomach or the esophagus or with pyloric stenosis due to ulcer and of some with intestinal obstruction, the effects of malnutrition and dehydration are frequently underestimated. It would therefore seem that, while serial hematocrit and protein determinations are of value, more thought and attention should be given the total circulating levels.

In the aforementioned patients and in approximately 15 other such patients a marked difference was noted in the convalescent period between those who were treated carefully with plasma, blood and physiologic solution of sodium chloride and those who were given fluids and transfusions without the same consideration. In almost every instance an uncomplicated postoperative course was experienced when careful studies of fluid balance were carried out.

It is apparent that this series of cases is not large, but from these and from other cases which have been followed the conclusions seem justified.

#### SUMMARY

From the cases presented it is evident that the hematocrit value and the plasma protein concentration may be near normal even when a relatively large deficit in the total number of red blood cells or the total circulating plasma protein exists. Thus, dehydration may be severe when a normal hematocrit value, plasma chloride level or protein con-

23. Scudder, J.: *Shock: Blood Studies as a Guide to Therapy*, Philadelphia, J. B. Lippincott Company, 1940.

24. Peters, J. P.; Wakeman, A. M., and Eisenman, A. J.: *The Plasma Proteins in Relation to Blood Hydration: III. The Plasma Proteins in Malnutrition*, J. Clin. Investigation 3:491-495, 1927.

centration is present, and hence these determinations are of limited usefulness and may even be confusing, especially if serial levels are not obtained.

The use of large amounts of physiologic solution of sodium chloride (2,500 to 7,000 cc.) postoperatively in malnourished patients to counteract or prevent dehydration may provoke serious complications (pulmonary edema, atelectasis and bronchopneumonia).

The total circulating plasma proteins frequently fall to a level of clinical importance (from 6 to 50 per cent below normal in the series of patients presented). Several observations would seem to indicate that dehiscence or healing of wounds would bear a much closer relation to catabolism or anabolism of proteins than to the concentration of proteins in the plasma.

In the treatment of such conditions it seems desirable to replenish not only the plasma proteins but also the tissue proteins. If adequate calories cannot be consumed orally, intravenous or intrasternal alimentation should be resorted to.

Amino acids can be employed parenterally as the only source of nitrogen to maintain positive nitrogen balance, and when adequate amounts are given along with sufficient calories, an increase in the total circulating plasma proteins can be obtained.

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# AN ANATOMIC STUDY OF VENOUS VARIATIONS AT THE FOSSA OVALIS

THE SIGNIFICANCE OF RECURRENCES FOLLOWING LIGATIONS

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Although this paper primarily concerns itself with the variations of the tributaries of the vena saphena magna at the saphenofemoral junction, the obvious application of this research to ligation of veins and to recurrences after treatment of varicose veins is apparent. The unequivocal value of high ligation is established. The popularity of this procedure and its widespread use, particularly by surgeons unfamiliar with the field of vascular surgery, account for the not uncommon failures and recurrences. A lack of knowledge of the anatomy of the venous drainage of the lower extremity is probably the greatest single cause of poor results. In view of the exploratory nature of the operations required because of common variations, it would not be amiss at this point to emphasize the fact that ligation of the saphenous vein is not an office procedure.

The material in this communication is based on the dissection in the fossa ovalis region of 100 lower extremities (50 cadavers).<sup>1</sup> The great number of variations should not be considered unusual, because it is known that venous patterns throughout the body are generally inconstant. Numerous variations have also been observed wherever an opening similar to the fossa ovalis is present—note the abnormalities in the popliteal and other similar regions. The striking finding in these dissections was the frequent occurrence of accessory saphenous and prominent lateral superficial femoral veins. This is decidedly at variance with the usual textbook picture depicting these as small, multiple veins draining into the vena saphena magna far below the fossa ovalis.<sup>2</sup> This venous

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1. Glasser, S. T.: Variations of the Tributaries of the Saphena Magna at the Sapheno-Femoral Junction: Abstract of Demonstration, *Anat. Rec.* 82:93 (March 25) 1942.

2. (a) Piersol, G. A.: *Human Anatomy*, ed. 4, Philadelphia, J. B. Lippincott Company, 1913, pp. 916-917. (b) Spalteholz, H. W.: *Atlas of Human Anatomy*, edited by L. F. Barker, ed. 4, Philadelphia, J. B. Lippincott Company, 1923, vol. 2. (c) Gray, H.: *Anatomy of the Human Body*, edited by W. H. Lewis, ed. 22, Philadelphia, Lea & Febiger, 1930, pp. 734-735. (d) Deaver, J. B.: *Surgical Anatomy*, Philadelphia, P. Blakiston's Son & Co., 1903, vol. 3, p. 557. (e) Quain,

*(Footnote continued on next page)*

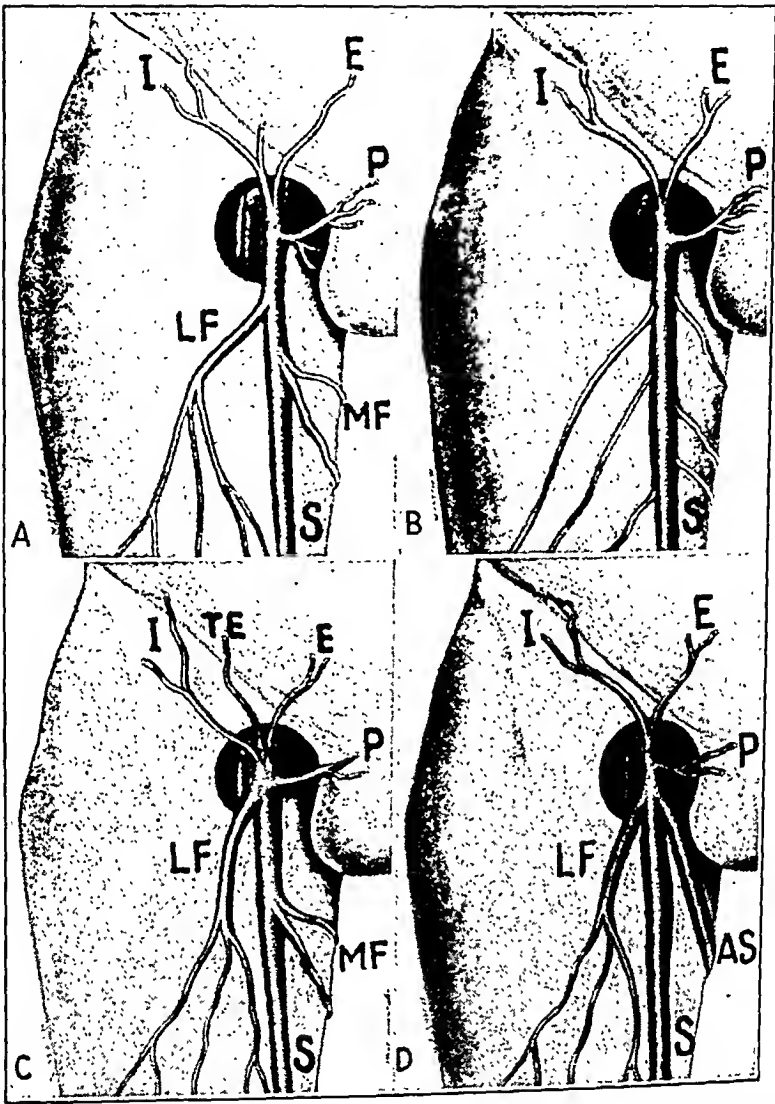


Fig. 1.—*A*, Average “textbook” diagram of venous drainage at fossa ovalis. Incidence 37 per cent. *B*, Multiple divisions of the medial and lateral femoral veins of small caliber. Incidence 6 per cent. *C*, The large lateral superficial femoral vein drains into the fossa ovalis. The inconstant thoracoepigastric vein drains into the vena saphena magna instead of into the femoral vein. Incidence 2 per cent. *D*, The lateral superficial femoral and the accessory saphenous vein drain into the fossa ovalis. Incidence 2 per cent. Abbreviations used in this and in the following illustrations are as follows: *I*, superficial circumflex iliac vein; *E*, superficial epigastric vein; *P*, superficial external pudendal vein; *LF*, lateral superficial femoral vein; *MF*, medial superficial femoral vein; *AS*, accessory saphenous vein; *SS*, double saphenous vein; *S*, vena saphena magna; *TE*, thoracoepigastric vein; *F*, femoral vein.

J.: Elements of Anatomy, ed. 9, London, Longmans, Green & Co., 1882, vol. 1, pp. 519-520. (f) Cunningham, D. J.: Cunningham's Text Book of Anatomy, edited by J. C. Brash and E. B. Jamieson, ed. 7, London, Oxford University Press, 1937, pp. 1270-1272. (g) Ochsner, A., and Mahorner, H.: Varicose Veins, St. Louis, C. V. Mosby Company, 1939.

pattern, occurring in only 37 per cent of our series, is illustrated in figure 1 *A*. If figures 1 *B* and 4 *D* are added to the preceding group, the total number of cases in which "insignificant" medial and lateral superficial femoral veins were present would be 44 per cent. In other words, more than 50 per cent of the dissections illustrated prominent superficial

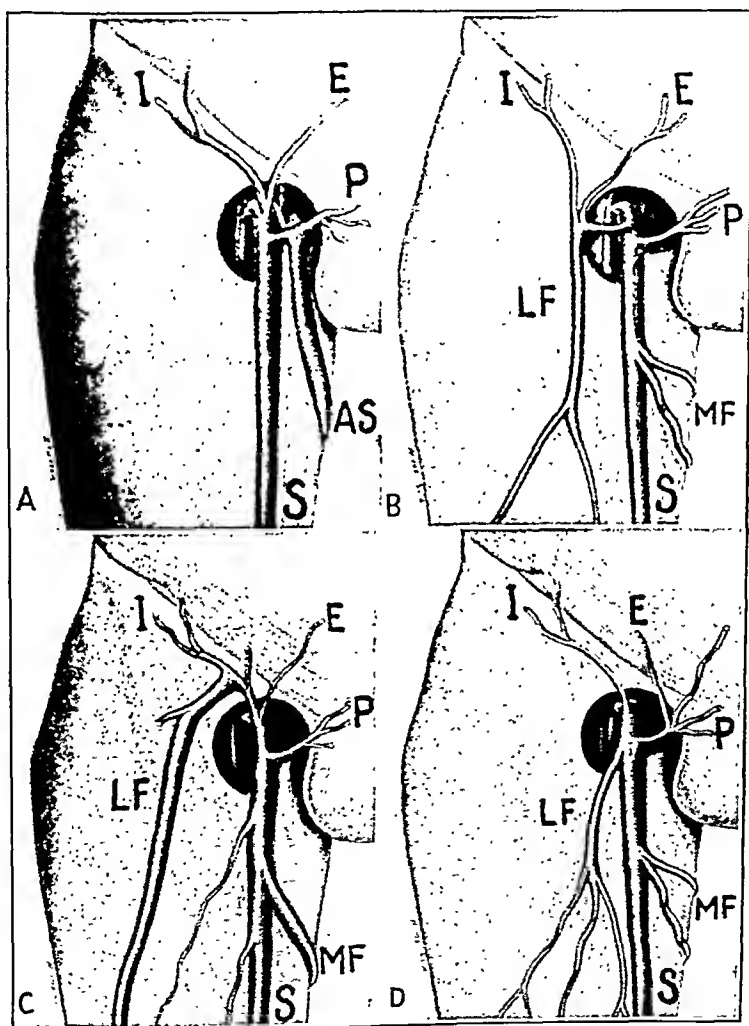


Fig. 2.—*A*, The accessory saphenous vein forms a common stem with the superficial external pudendal vein before joining the vena saphena magna. Incidence 6 per cent. *B*, A common trunk formed by the lateral superficial femoral, superficial circumflex iliac and superficial epigastric veins drains into the fossa ovalis. Incidence 9 per cent. *C*, A common trunk formed by the lateral superficial femoral and the superficial circumflex iliac vein drains into the fossa ovalis. Incidence 9 per cent. *D*, The superficial epigastric and the superficial external pudendal vein form a common trunk. A large lateral superficial femoral vein is present. Incidence 2 per cent.



femoral veins.<sup>28</sup> The significance of these so-called variations becomes of major importance when an analysis of recurrences is considered. The higher tributaries are of less importance as causes of failure in treatment, except in those infrequent instances in which the superficial femoral

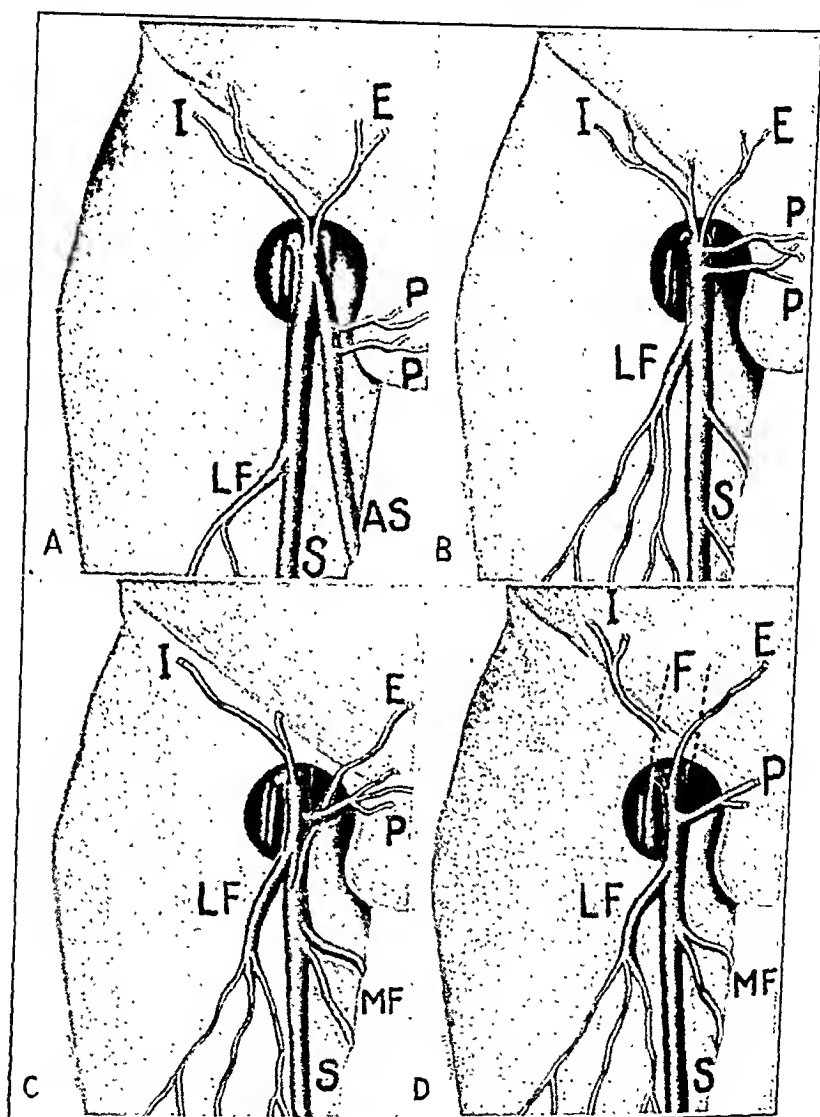


Fig. 3.—*A*, An accessory saphenous vein is present. Note the drainage of double superficial external pudendal veins. Incidence 1 per cent. *B*, Double superficial external pudendal veins drain into the fossa ovalis. Incidence 3 per cent. *C*, The superficial epigastric vein drains into the vena saphena magna below the fossa ovalis. Incidence 3 per cent. *D*, The superficial circumflex iliac vein drains into the femoral vein. Incidence 1 per cent.

veins form separate junctions with the pudendal, circumflex iliac or epigastric veins (figs. 2 *A*, 2 *B*, 2 *C*, 4 *B* and 5 *A*). A double saphenous

vein was found in only 3 per cent of the specimens (fig. 5 *B*). The incidence of direct drainage into the femoral vein of the higher tributaries collectively or singly was 16 per cent (figs. 3 *D*, 4 *A*, 4 *B*, 4 *C*, 4 *D* and 5 *A*). In one instance (fig. 5 *C*) the vena saphena magna was found to pierce the deep fascia and join the femoral vein about 1 inch (2.5 cm.)

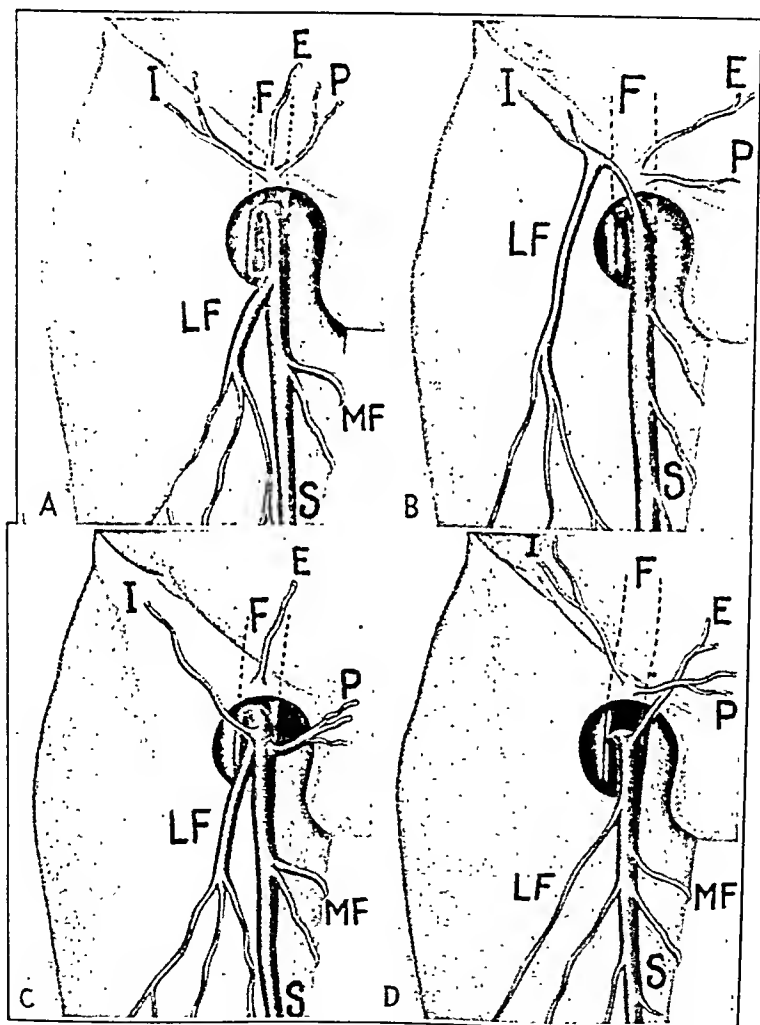


Fig. 4.—*A*, All high collateral veins drain directly into the femoral vein. Incidence 6 per cent. *B*, The lateral femoral and the superficial circumflex iliac vein form a common trunk. The other high collateral veins drain directly into the femoral vein. Incidence 1 per cent. *C*, The lateral femoral vein drains into the fossa ovalis. The superficial epigastric vein drains directly into the femoral vein. Incidence 6 per cent. *D*, Note the small caliber multiple medial and lateral superficial femoral veins. The superficial circumflex iliac and the superficial external pudendal vein drain directly into the femoral vein. Incidence 1 per cent.

below the fossa ovalis. This is a rare occurrence and has been described by Ochsner and Mahorner.<sup>22</sup>

The clinical application of this study to the patients with recurrences reoperated on in our institution has not been thoroughly studied. Such a review is intended for a subsequent report. Most patients for whom a

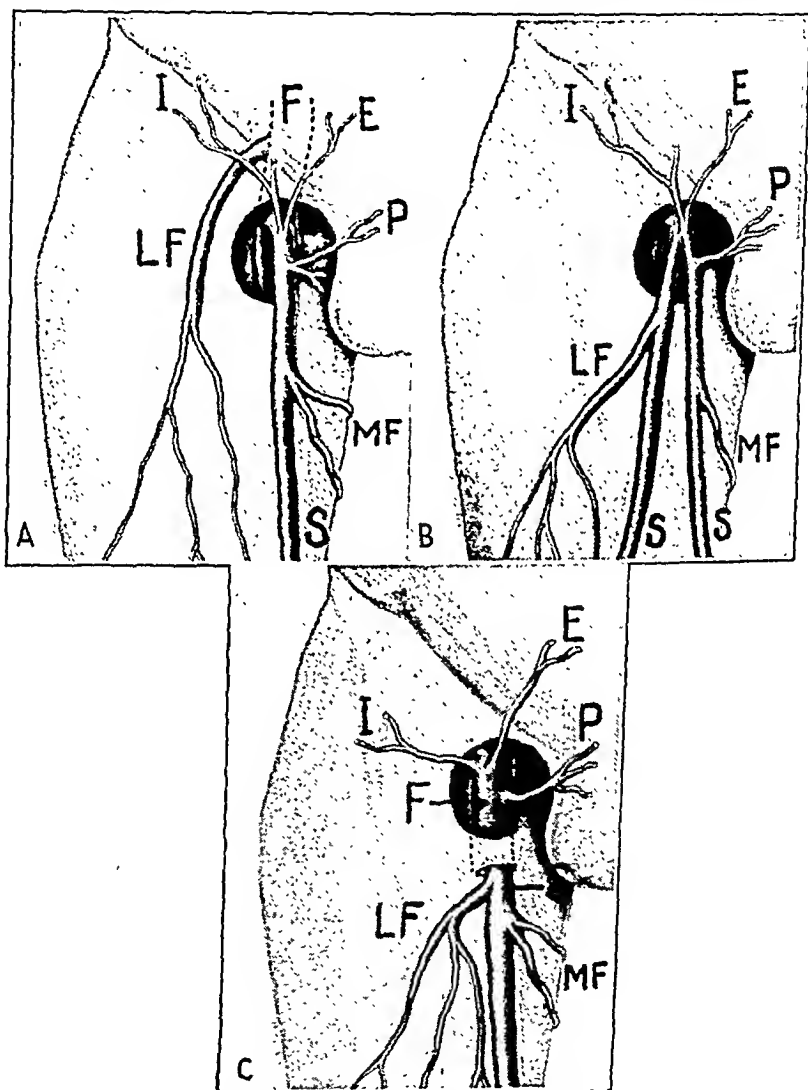


Fig. 5.—*A*, The lateral superficial femoral vein drains directly into the femoral vein. Incidence 1 per cent. *B*, A double vena saphena magna with joining at the fossa ovalis. Incidence 3 per cent. *C*, The saphena magna pierces the deep fascia to enter the femoral vein about 1 inch below the fossa ovalis. Incidence 1 per cent.

secondary operation was deemed necessary declined it. In those patients who permitted a second exploration, the presence of a patent medial (accessory) or a lateral superficial femoral vein was noted. There were

no examples of recurrence due to failure in ligation of the higher tributaries at the time of the primary operation. A finding of interest was the complaint of persistent pain which was relieved after the secondary operation. The mechanism of this finding is problematic, but it may possibly be due to reflex venospasm.

Another observation of importance is the dislocation in position and course of the tributaries in the presence of enlarged saphenous glands. Operative manipulation in these cases was found to be especially painful. The hypertrophied glands nearly always displaced the vena saphena magna medially.

Over 500 ligations have been performed in our peripheral vascular clinic. A proper follow-up of these patients will be made to determine the value of the aforementioned statements.

#### SUMMARY

An anatomic study of 100 dissections of the lower extremity in the region of the fossa ovalis with particular attention to the variations of the tributaries of the vena saphena magna is discussed.

Variations of the superficial femoral veins are probably the chief causes of recurrences following faulty primary ligations for the treatment of varicose veins.

The presence of pain in cases with recurrence seems to be frequent.

The presence of hypertrophied saphenous glands causes dislocation of the tributaries and also makes operative manipulation painful.

# INTRAVENOUS USE OF VITAMIN K<sub>1</sub> OXIDE

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The clinical importance of parenteral therapy with vitamin K has become well established. The most prolonged improvements in prothrombin clotting time so far reported have followed the intravenous administration of either synthetic vitamin K<sub>1</sub> or 2-methyl-1,4-naphthoquinone (menadione). The chemical reactivity and the toxicity of menadione as described by Fieser<sup>1</sup> make it less desirable for general use than vitamin K<sub>1</sub>. A single dose of one of these drugs can restore and maintain normal blood prothrombin levels for periods as long as two or three weeks.<sup>2</sup> Some inconvenience is caused by their lack of solubility in water and their sensitivity to ultraviolet rays. This has led to the continued use of water-soluble preparations; the effects of these are of much shorter duration, so that repeated injection is required for prolonged effect.

After the synthesis of vitamin K<sub>1</sub>, Fieser<sup>3</sup> postulated that this light-sensitive vitamin probably did not exist as the quinone in the green alfalfa leaf from which it had been isolated. He suggested that vitamin K<sub>1</sub> may be present in the green leaf as its oxide. Tishler, Fieser and Wendler<sup>4</sup> synthesized the oxide and found it to be readily reducible

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From the Medical Service, Peter Bent Brigham Hospital, and the Surgical Service, Beth Israel Hospital.

This investigation was aided by a grant from the Proctor Fund, Department of Medicine, Harvard Medical School.

1. Fieser, L. F.: *Ann. Int. Med.* **15**:648, 1941. According to J. V. Scudiff (Proc. Soc. Exper. Biol. & Med. **50**:16-17, 1942), when menadione is added to whole, unclotted blood it causes a pronounced formation of methemoglobin, and the drug is rapidly converted to some other substance, with marked loss in anti-hemorrhagic activity.

2. (a) Frank, H. A.; Hurwitz, A., and Seligman, A. M.: *New England J. Med.* **221**:975, 1939. (b) Seligman, A. M.; Hurwitz, A.; Frank, H. A., and Davis, W. A.: *Surg., Gynec. & Obst.* **73**:686, 1941.

3. Fieser, L. F.: *J. Am. Chem. Soc.* **61**:2559, 1939; footnote 1.

4. Tishler, M.; Fieser, L. F., and Wendler, N. L.: *J. Am. Chem. Soc.* **62**:2866, 1940.

to the hydroquinone of vitamin K<sub>1</sub>. Fieser, Tishler and Sampson<sup>5</sup> found the oxide to be three times as stable as the quinone on exposure to ultraviolet light and "hardly distinguishable" from the vitamin itself in assays on chicks. These workers were impressed with a similarity in properties between the synthetic oxide and a colorless fraction isolated from alfalfa by Fernholz, Ansbacher and co-workers.<sup>6</sup>

Because of the ease of preparation of the oxide from vitamin K<sub>1</sub> and its stability to ultraviolet rays, it was felt that the substance merited clinical trial. Although the oxide, like the vitamin itself, is not soluble in water, it was found that a stable suspension of therapeutic doses suitable for intravenous injection could be made in volumes as small as 10 cc. This seemed to increase the likelihood that the oxide would be a more generally useful agent for intravenous therapy with vitamin K. This paper reports the intravenous use of synthetic vitamin K<sub>1</sub> oxide.<sup>7</sup>

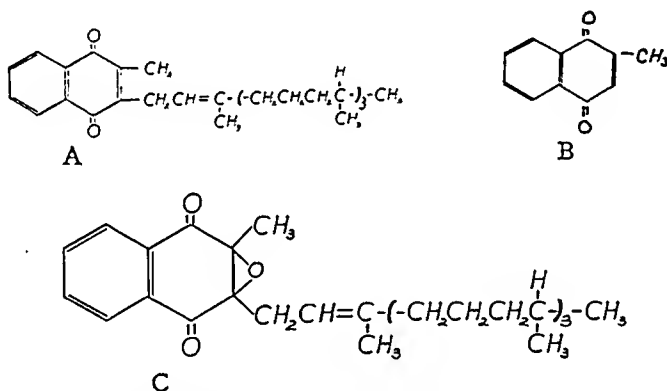


Chart 1.—Structural formulas for: A, vitamin K<sub>1</sub>; B, 2-methyl-1,4-naphthoquinone (menadione); C, vitamin K<sub>1</sub> oxide.

#### METHOD

Vitamin K<sub>1</sub> oxide can be prepared in liter volume for intravenous administration as a colloidal suspension by the method already described for vitamin K<sub>1</sub>.<sup>2</sup> However, it was found that stable suspensions of the oxide in solutions of dextrose or sodium chloride (remaining homogeneous for at least two months) could be made more concentrated than in the case of vitamin K<sub>1</sub>, a preliminary announcement of this finding having been made by Fieser.<sup>1</sup> It was found convenient to draw 10 mg. of the oxide dissolved in 3 cc. of alcohol into a syringe containing 10 cc. of

5. Fieser, L. F.; Tishler, M., and Sampson, W. L.: *J. Biol. Chem.* **137**:659, 1941.

6. Ansbacher, S.; Fernholz, E., and MacPhillamy, H. B.: *Proc. Soc. Exper. Biol. & Med.* **42**:655, 1939. Fernholz, E.; Ansbacher, S., and Moore, M. L.: *J. Am. Chem. Soc.* **61**:1613, 1939.

7. Provided by Prof. Louis F. Fieser, Harvard University.

sterile physiologic solution of sodium chloride immediately before injection. For sterilization sealed ampules of the oxide in alcohol were autoclaved before being mixed with sterile solution of sodium chloride. No untoward reaction followed the administration of these suspensions.

The prothrombin determination of Quick<sup>8</sup> was employed. The normal range was thirteen and a half to seventeen seconds.

### RESULTS

CASE 1.—M. M., a 45 year old woman with a past history of injury of the common duct, choledochoduodenostomy and intermittent jaundice, chills and fever of two years' duration, entered the hospital for relief of obstruction of the common duct. Examination revealed jaundice and a markedly enlarged liver. Laboratory data on admission were as follows: The urine contained bile. The stools were brown. A guaiac test gave negative results. The red blood cell count was 4,300,000, the hemoglobin content 70 per cent and the white blood cell count 10,400, with 72 per cent polymorphonuclear leukocytes. The nonprotein nitrogen content of the blood was 29 mg. per hundred cubic centimeters. The icterus index was 49.

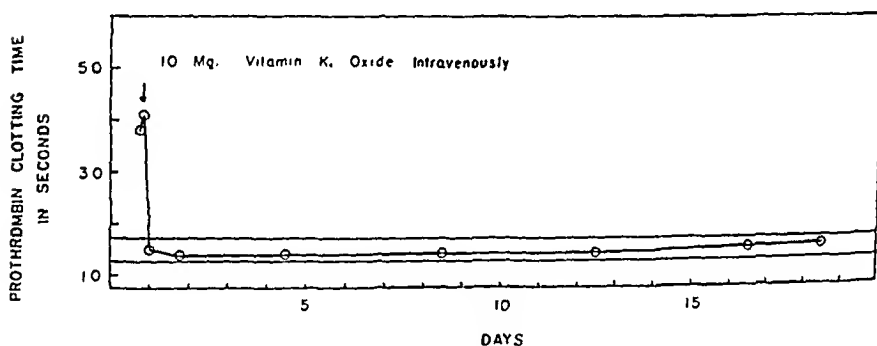


Chart 2.—Course of prothrombin clotting times for patient in case 1.

The protein content of the serum was 7.7 Gm. per hundred cubic centimeters, with albumin 3.7 Gm. and globulin 4 Gm. The cholesterol content was 430 mg. per hundred cubic centimeters. The blood diastase content was normal. The bleeding time was three and a half minutes (Duke test); clotting time, fourteen minutes (test tube); the prothrombin clotting time, ninety seconds.

On the day following admission to the hospital the patient received 6 mg. of vitamin K<sub>1</sub> oxide intravenously. When laparotomy was performed a week later, the bleeding time was six minutes and the prothrombin clotting time sixteen and a half seconds. Complete obliteration of the lower portion of the common duct was found. Choledochoduodenostomy was reestablished after mobilization of the proximal segment; external drainage was afforded, and biopsy of the liver was done. Convalescence was uneventful, and the patient was discharged from the hospital with the T tube clamped on the fifteenth postoperative day. No unusual bleeding was noted at operation or thereafter. Following discharge the patient's jaundice

8. Quick, A. J.: Nature of Bleeding in Jaundice, J. A. M. A. 110:1658 (May 14) 1938.

disappeared and her liver diminished in size. The biopsy of the liver revealed acute hepatitis and obstructive biliary cirrhosis.

The course of the prothrombin clotting times is shown in chart 2. The rapid response and the prolonged action following a single dose of the oxide in this patient with biliary obstruction and hepatitis are shown.

CASE 2.—H. B., a 59 year old woman with a past history of radical mastectomy for carcinoma six years before, entered the hospital because of the gradual development of jaundice, malaise and nausea in the two months preceding admission. Examination revealed extreme jaundice, bleeding excoriations of the skin, numerous ecchymoses, ascites, a large, nontender liver and bloody discharge from the rectum. The left breast was absent, and there was a nodule in the mastectomy scar. Laboratory data on admission were as follows: The urine contained bile. The red blood cell count was 3,500,000, the hemoglobin content 75 per cent and

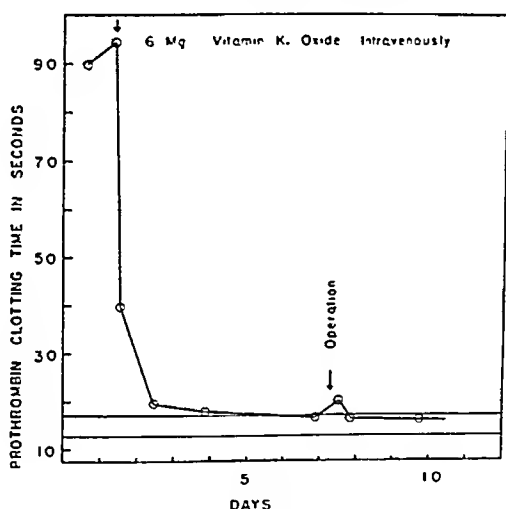


Chart 3.—Course of prothrombin clotting times for patient in case 2.

the white blood cell count 6,000 with 85 per cent polymorphonuclear leukocytes. The nonprotein nitrogen content of the blood was 36 mg. per hundred cubic centimeters. The protein content of the serum was 5.8 Gm. per hundred cubic centimeters, with albumin 2.8 Gm. and globulin 3 Gm. The icterus index was 149. The stools were gray or black. A guaiac test gave positive results. The prothrombin clotting time was thirty-eight seconds. There was roentgen evidence of pulmonary metastases, and tumor cells were found in the paracentesis fluid. One hour after admission the patient received 10 mg. of vitamin K<sub>1</sub> oxide intravenously. All evidence of generalized bleeding disappeared. The patient became progressively worse and died on the twenty-first day of hospitalization. Permission for postmortem examination was not obtained.

The course of the prothrombin clotting time is shown in chart 3. A rapid and prolonged effect from a single dose of the oxide was obtained in this patient with obstructive jaundice from metastatic carcinoma. The more rapid response to the vitamin in this case as compared with that in the previous one is probably attributable to a less severe degree of hepatic impairment.



## SUMMARY

Vitamin K<sub>1</sub> oxide, synthesized by Fieser and co-workers and shown to be three times as stable as vitamin K<sub>1</sub> to ultraviolet rays, has been tested clinically for the first time.

A convenient method for preparing the synthetic vitamin K<sub>1</sub> oxide for intravenous administration is described.

A single intravenous dose of vitamin K<sub>1</sub> oxide was found to produce the rapid response and the prolonged action noted with vitamin K<sub>1</sub>.<sup>2b</sup>

Merck & Co., Inc., provided a large supply of vitamin K<sub>1</sub> oxide.

330 Brookline Avenue.

# CONCENTRATION OF PROCAINE IN THE CEREBROSPINAL FLUID OF THE HUMAN BEING AFTER SUBARACHNOID INJECTION

## THIRD REPORT

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BROOKLYN

Elsewhere my associates and I<sup>1</sup> have reported on the concentration of procaine in the subarachnoid space during spinal anesthesia in patients in the Trendelenburg position. The reports were based on the analysis of samples taken at various intervals of time from three groups of adult patients, at the site of injection, from a site three interspaces above and from the cisterna magna. The first group of 122 patients received 150 mg. of procaine hydrochloride dissolved in 3.5 cc. of cerebrospinal fluid; the second group of 156 patients received 300 mg. dissolved in 3.5 cc., and the third group of 143 patients received 300 mg. dissolved in 7 cc. All injections were made between the second and the third lumbar vertebra, and the patients were immediately placed in the Trendelenburg position. After this samples were taken.

At the moment of injection the concentration at the site of injection is at its maximum, namely, the concentration of the injected fluid (43 mg. per cubic centimeter). This falls rapidly in the first few minutes. At the moment of injection the concentration of procaine three interspaces above the site of injection is 0, but it rises rapidly in the first four minutes. The maximum concentration here is never above 4 mg. per cubic centimeter, and at no moment does it equal the level at the site of injection. From then on the concentrations at the site of injection and three interspaces above decrease at approximately the same rate, and at no time is the concentration in the dorsal region as great as in the lumbar. The highest concentration in the cisterna is never greater than 0.21 mg. and frequently less than 0.02 mg. per cubic

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From the Richard Morton Koster Research Laboratory.

1. (a) Koster, H.; Shapiro, A., and Leikensohn, A.: Spinal Anesthesia: Procaine Concentration Changes at the Site of Injection in Subarachnoid Anesthesia, *Am. J. Surg.* **33**:245-248 (Aug.) 1936; (b) Concentration of Procaine in the Cerebrospinal Fluid of the Human Being After Subarachnoid Injection, *Arch. Surg.* **37**:603-608 (Oct.) 1938. (c) Koster, H.; Shapiro, A., and Warshaw, R.: Concentration of Procaine in the Cerebrospinal Fluid of the Human Being After Subarachnoid Injection, *ibid.* **39**:97-103 (July) 1939.

centimeter. Comparative analysis of these data did not support the assumption of many authors<sup>2</sup> that the Trendelenburg position causes concentrated solutions of procaine hydrochloride to flow down to the cisterna magna as do colored solutions in inanimate models.

It is obvious that the information obtained regarding the concentration of procaine in patients under the circumstances just described could be used as a standard for comparison. It was then deemed advisable to repeat the experiment with patients in the Fowler position to determine whether the concentration curves would be significantly changed by the change in posture.

#### METHOD

One hundred and twenty-eight adult patients received an injection of procaine hydrochloride dissolved in 3.5 cc. of cerebrospinal fluid at the interspace between the second and the third lumbar vertebra. The patients were then placed in the Fowler position at angles of 10 degrees. At different intervals after the injection, samples of 1 cc. of cerebrospinal fluid were withdrawn from various patients. From a group of 55 patients samples were withdrawn from the site of injection. From another group, of 56 patients, samples were withdrawn three interspaces cephalad. From a third group, of 17 patients, samples were withdrawn from the cisterna magna. The concentration of procaine in these samples was determined in most cases in duplicate or triplicate by the micromethod previously described,<sup>3</sup> with an error not over 10 per cent.

#### RESULTS

The concentrations of procaine in the spinal fluid at the site of injection, at a site three interspaces above and in the cisterna magna in patients in the Fowler position are shown graphically in charts 1, 2 and 3.

At the moment of injection the maximum concentration at the site of the injection is that of the injected solution (43 mg. per cubic centimeter). This falls rapidly, so that at the end of ten minutes the level of concentration is in the neighborhood of 2 mg. per cubic centimeter. The level of concentration falls slowly thereafter until the anesthesia wears off.

At the moment of injection the level of concentration three interspaces above the site of injection is 0, but it then mounts rapidly in the

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2. Pitkin, G. H.: Controllable Spinal Anesthesia, *Am. J. Surg.* **5**:537-553 (Dec.) 1928. Co Tui, F. W.: Further Studies in Subarachnoid Anesthesia, *Anesth. & Analg.* **13**:143 (July-Aug.) 1934. Vehrs, A. R.: Problems in the Hydrodynamics of Analgesics in the Subarachnoid Fluid of Man: Diazotized Novocaine in Artificial Dural Sacs, *West. J. Surg.* **43**:16-32 (Jan.) 1935. Babcock, W. W.: Spinal Anesthesia in Fact and Fancy, *Surg., Gynec. & Obst.* **59**:94-100 (July) 1934.

3. Koster, H.; Shapiro, A., and Posen, E.: A Micromethod for the Quantitative Determination of Procaine in Cerebrospinal Fluid, *J. Lab. & Clin. Med.* **21**:1096-1098 (July) 1936.

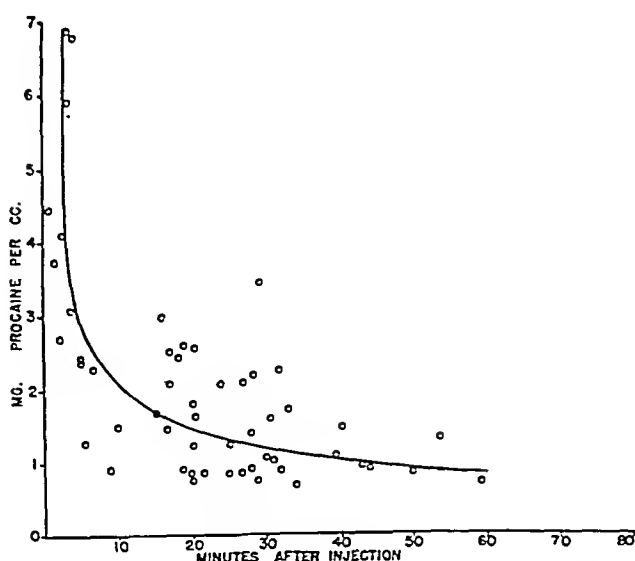


Chart 1.—Concentration of procaine in the cerebrospinal fluid at the site of injection in different patients at various intervals after the injection of the anesthetic. The patients were in the Fowler position.

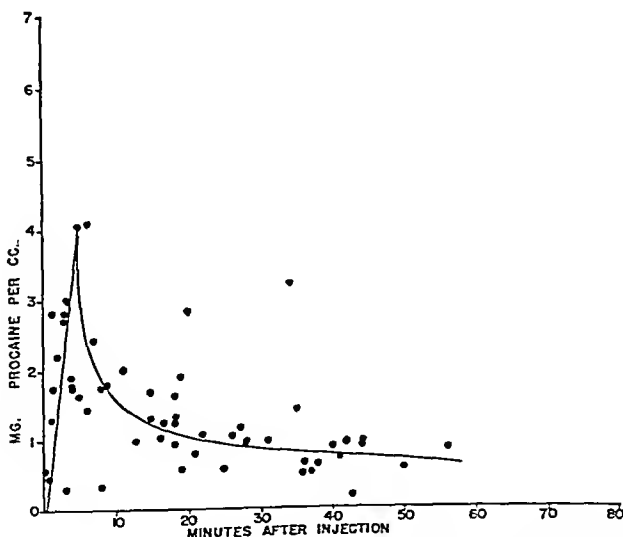


Chart 2.—Concentration of procaine in the cerebrospinal fluid three interspaces above the site of injection in different patients at various intervals after the injection of the anesthetic. The patients were in the Fowler position.

first five minutes to the level of 4 mg. per cubic centimeter. After reaching a peak it falls rapidly for approximately four or five minutes and then more slowly until the anesthesia disappears. At all times, however, the concentration here maintains a slightly lower level than that at the site of injection.

Samples taken from the cisterna magna in patients in the Fowler position never showed concentration values greater than 0.18 mg. per cubic centimeter and frequently less than 0.02 mg. per cubic centimeter.

#### COMMENT

With patients in a 10 degree Fowler position the cisterna magna is at a higher level than the lumbar portion of the subarachnoid space.

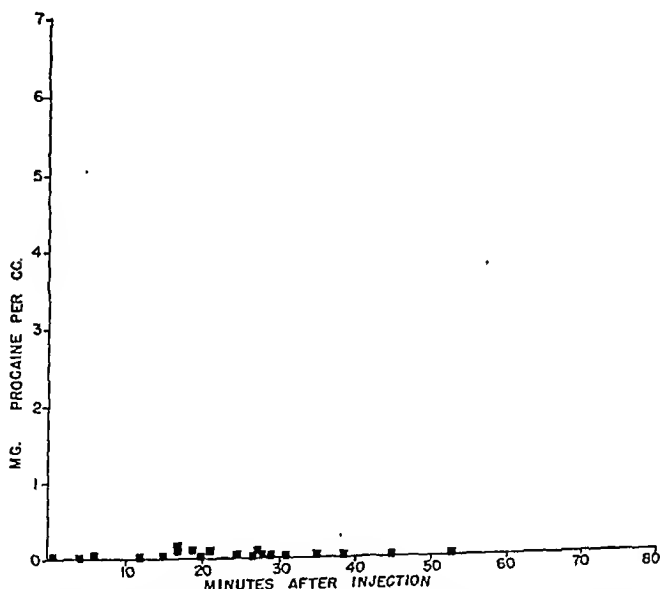


Chart 3.—Concentration of procaine in the cerebrospinal fluid in the cisterna cerebellomedullaris in different patients at various intervals after the injection of the anesthetic. The patients were in the Fowler position.

If the distribution of the injected anesthetic solution is significantly affected by gravity, it might be expected that no anesthetic would be found in the cisterna magna. It might also be expected that the concentration values of samples taken at the site of injection and from a site three interspaces above would vary significantly from samples similarly obtained from patients in the Trendelenburg position. The difference between the two positions is represented by an angle of between 15 and 18 degrees.

In the Fowler position procaine is found in the cisterna magna in small amounts. The values are not significantly different from those

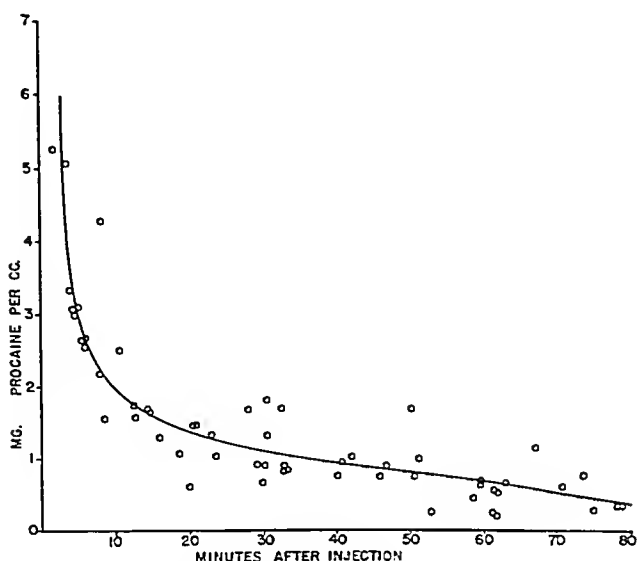


Chart 4.—Concentration of procaine in the cerebrospinal fluid at the site of injection in different patients at various intervals after the injection of the anesthetic. The patients were in the Trendelenburg position.

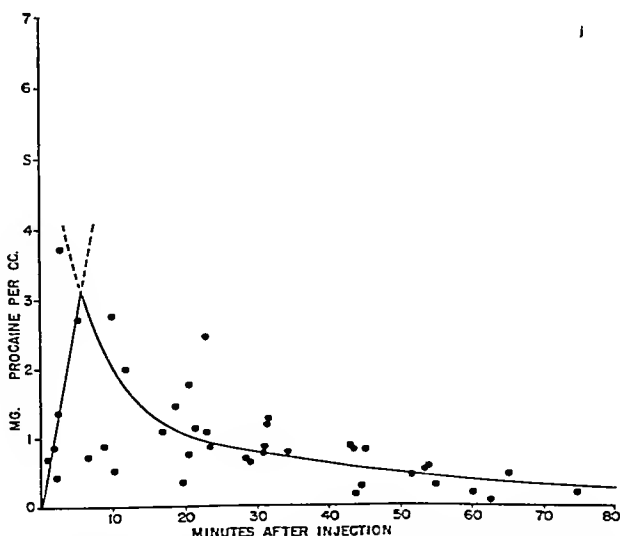


Chart 5.—Concentration of procaine in the cerebrospinal fluid three interspaces above the site of injection in different patients at various intervals after the injection of the anesthetic. The patients were in the Trendelenburg position.

similarly obtained for patients in the Trendelenburg position. Some explanation might be found for the presence of procaine in the cisterna magna in patients in the Fowler position, a presence which serves to contradict the assumption that concentrated solutions of procaine hydrochloride flow to dependent parts of the subarachnoid space as do colored solutions in glass models. However these findings and the existence of similar amounts of procaine in patients in the Trendelenburg position seem to indicate that for the degrees of change from the true horizontal position used in these experiments gravitational displacement of the injected solution is negligible.

For convenience of comparison the data on the concentration of procaine at the site of injection, three interspaces above and in the cisterna

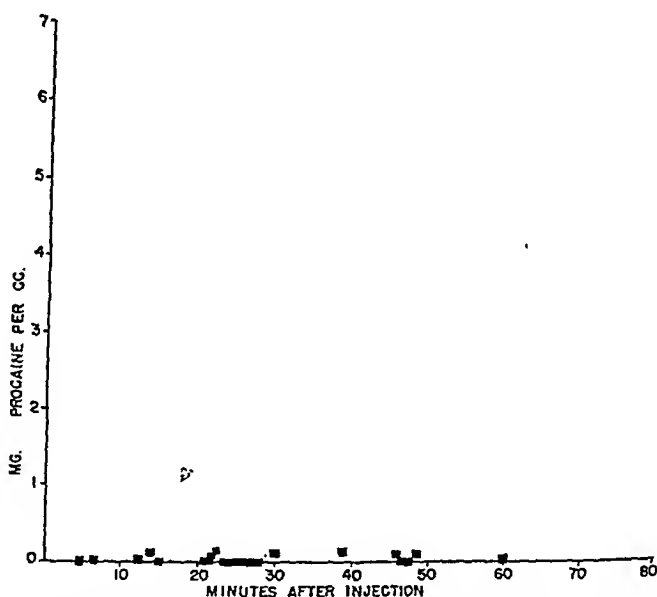


Chart 6.—Concentration of procaine in the cerebrospinal fluid in the cisterna cerebellomedullaris in different patients at various intervals after the injection of the anesthetic. The patients were in the Trendelenburg position.

magna in patients in the Trendelenburg position are graphically reproduced<sup>2b</sup> in charts 4, 5 and 6. It can be seen that there is no significant difference between the concentration curves of patients in the Fowler and in the Trendelenburg position. This seems to indicate that the factors responsible for the spread of the anesthetic in the subarachnoid space are not noticeably affected by such changes in position as occurred in these experiments. It also indicates that within these limits concentrated solutions of procaine hydrochloride do not settle into dependent portions of the subarachnoid space as do colored solutions in inanimate models.

## LESIONS OF THE SUPRASPINATUS TENDON

## DEGENERATION, RUPTURE AND CALCIFICATION

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The purpose of this paper is to make a survey of the literature on lesions of the tendons of the short rotator muscles of the shoulder, namely, the supraspinatus, infraspinatus, teres minor and subscapularis. As has been pointed out by Codman,<sup>1</sup> lesions of the shoulder tendons, notably rupture of the supraspinatus tendon, are significant because of the long duration of the disability produced when they are not recognized early. This is particularly important in the laboring classes, for the disability produced by rupture of the supraspinatus tendon may be sufficient to prevent a laborer from working for two years.<sup>2</sup>

## I. ANATOMIC CONSIDERATIONS

*Gross Anatomy.*—The anatomy of the shoulder joint will be considered briefly in order to give a clear concept of the subacromial bursa, the tendons of the short rotator muscles of the shoulder, namely the supraspinatus, infraspinatus, teres minor and subscapularis, and the tendon of the long head of the biceps muscle. If the anatomy and function of these structures are clearly pictured, the understanding of the conditions affecting them is greatly enhanced.

The subacromial bursa is a synovial bursa occurring beneath the deltoid muscle, the coracoacromial ligament and the acromion and intervening between these structures and the supraspinatus tendon.<sup>3</sup> The bursa is roughly circular in outline, fitting equally over the ligaments and their insertions into the head of the humerus, like a skull cap. Codman<sup>1b</sup> remarked that "the first time one cuts into a normal bursa one is startled to find how much the base looks like the shoulder joint itself. One cannot distinguish by sight the line between the portions which are on bone, or on tendon beneath the shiny base." The bursa increases in size with age, being

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\* Fellow in Medicine of the National Research Council; Surgeon Lieutenant, Royal Canadian Navy (VR).

1. Codman, E. A.: (a) Some Points on the Diagnosis and Treatment of Certain Neglected Minor Surgical Lesions, Boston M. & S. J. **150**:371, 1904; (b) Stiff and Painful Shoulders: The Anatomy of the Subdeltoid or Subacromial Bursa and Its Clinical Importance; Subdeltoid Bursitis, *ibid.* **154**:613, 1906; (c) Bursitis Subacromialis or Periarthritis of the Shoulder Joint: Bursitis, *ibid.* **159**:533, 576, 615, 677 and 723, 1908; (d) Complete Rupture of the Supraspinatus Tendon: Operative Treatment with Report of Two Successful Cases, *ibid.* **164**:708, 1911; (e) On Stiff and Painful Shoulders, as Explained by Subacromial Bursitis and Partial Rupture of the Tendon of the Supraspinatus, *ibid.* **165**:115, 1911; (f) Obscure Lesions of the Shoulder: Rupture of the Supraspinatus Tendon, *ibid.* **196**:381, 1927; (g) Rupture of the Supraspinatus Tendon, Surg., Gynec. & Obst. **52**:579, 1931; (h) The Shoulder: Rupture of the Supraspinatus Tendon and Other Lesions in or About the Subacromial Bursa, Boston, The Author, 1934; (i) Rupture of Supraspinatus, Am. J. Surg. **42**:603, 1938.

2. Codman,<sup>1b,1</sup>

3. (a) Gray, H.: Anatomy, Descriptive and Applied, edited by T. B. Johnston, ed. 26, New York, Longmans, Green & Co., 1935. (b) Piersol, G. A.: Human Anatomy, Philadelphia, J. B. Lippincott Company, 1907, vol. 2. (c) Codman,<sup>1b,h</sup>



1.5 cm. in diameter in a newly born infant and 3 to 7 cm.<sup>4</sup> in diameter in a fully developed adult. Its function is to permit the upper end of the humerus with its capsule to glide easily under the coracoacromial ligament and the acromion during abduction.<sup>5</sup> The bursa has been considered to be indispensable in abduction and rotation of the humerus,<sup>5b</sup> but Moseley<sup>6</sup> has removed the bursa in 2 cases and had perfect function of the arm.

The origins of the four short rotator muscles can be reviewed in any textbook of anatomy. The important point is that their tendons flatten out and blend almost indistinguishably with the floor of the subacromial bursa and capsule of the shoulder joint.<sup>7</sup> The edges of the tendons of the four muscles approximate each other, and it is often difficult to tell where one stops and the next begins.<sup>8</sup> This fused structure Codman<sup>1b</sup> called "the musculo-tendinous cuff." The average length of the supraspinatus tendon on both the right and the left side is 2.25 cm.<sup>7b</sup>

The attachment of the tendons of the short rotator muscles takes place through most of the upper half of the sulcus, which is called the anatomic neck of the humerus. The heavier portions of the tendons are inserted on the facets situated on the greater tuberosity. Skinner<sup>9</sup> claimed that the muscular portion decreases with age and is replaced by fibrous tissue. This aponeurosis then fuses with the capsule of the shoulder joint. This view, however, is refuted by the work of Lindblom,<sup>10</sup> who found that the length of the tendon compared with the width of the head of the humerus was  $9:14 = 0.64$  (8 cases) in fetuses and children, and  $73:131 = 0.56$  (27 cases) in adults. Other measurements,<sup>7b</sup> of tendons showed no increase in length once adult life had been reached.

*Function.*—The functions of the short rotator muscles of the arm, especially the supraspinatus, have been the subject of a great deal of controversy. Each author has to a certain extent been correct in his interpretation, and it is possible to combine their various views to give a complete picture. It must be realized at the outset that the function of any muscle depends not only on the direction of its force but on its training. The anatomy of the insertion of the short rotator cuff is such that all the muscles composing it must work together. Stevens<sup>11</sup> stated that the subscapularis muscle on one side and the infraspinatus and teres minor muscles on the other act as a sling around the anatomic neck of the humerus, keeping the head of the humerus against the glenoid cavity during abduction. Since their line of pull passes through the fulcrum of the lever, their action does not hinder abduction.

The supraspinatus tendon acts as an abductor of the arm.<sup>12</sup> Codman found that when the deltoid is paralyzed by a lesion of the circumflex nerve the patient

4. (a) Wilson, P. D.: Complete Rupture of the Supraspinatus Tendon, *J. A. M. A.* **96**:433 (Feb. 7) 1931. (b) Codman.<sup>1b</sup>

5. Codman.<sup>1b, h</sup> Wilson.<sup>4a</sup>

6. Moseley, H. F.: Personal communication to the author.

7. (a) McKeown, E. G.: Shoulder Joint Injury: Rupture of the Supraspinatus Tendon, *Journal-Lancet* **55**:38, 1935. (b) Wilson, C. L., and Duff, G. L.: A Pathological Study of Degeneration and Rupture of the Supraspinatus Tendon, to be published. (c) Codman.<sup>1b</sup> Wilson.<sup>4a</sup>

8. Laird, R. C.: Complete Rupture of the Supraspinatus Tendon, *Bull. Acad. Med., Toronto* **14**:111, 1941. Footnote 7c.

9. Skinner, H. A.: Anatomical Considerations Relative to Rupture of the Supraspinatus Tendon, *J. Bone & Joint Surg.* **19**:137, 1937.

10. Lindblom, K.: On Pathogenesis of Ruptures of the Tendon Aponeurosis of the Shoulder Joint, *Acta radiol.* **20**:563, 1939.

11. Stevens, J. H.: Action of the Short Rotators of the Arm, *Am. J. M. Sc.* **138**:870, 1909.

12. (a) Duchenne, G. B. A.: Physiologie des mouvements démontrée à l'aide de l'expérimentation électrique et de l'observation clinique, Paris, J. B. Baillière & fils, 1867. (b) Johnston,

can still feebly abduct the arm. If he cannot, then operation of rupture of the supraspinatus.<sup>13</sup> Smith and Christensen<sup>12</sup> as have not concurred with this statement. Moseley,<sup>14</sup> by injecting iodine into a ruptured supraspinatus tendon and thus rendering that abduction is still possible but much weakened. The case of rupture of the supraspinatus tendon is therefore discussed by the authors<sup>15</sup> have contended that the supraspinatus muscle prevents the humerus from slipping up out of the glenoid cavity, but acting alone, the upward and inward pull of the supraspinatus would actually pull the greater tuberosity against the under arch. Codman<sup>16</sup> advanced the idea of "scapulo-humeral mechanism" meant that as the humerus and scapula move in abduction the direction of muscle pull changes, so that the supraspinatus muscle becomes an abductor and of a stabilizer but in different phases of abduction up to the horizontal position, and from there it acts as a stabilizer of the shoulder joint.

Martin<sup>16</sup> has pointed out that as the humerus is raised from the upright position it rotates laterally through 180 degrees. In the sagittal plane no rotation occurs. He showed that if the deltoid muscles raise the arm in the coronal plane, they also rotate it. It should be noted that abduction of the humerus occurs in the plane of the scapula<sup>17</sup> (not the plane of the trunk) and carries the arm laterally away from the trunk.

The tendon of the long head of the biceps muscle<sup>18</sup> as it ascends becomes encased in the synovial membrane of the shoulder joint through an opening in the capsular ligament. It then passes over the greater tuberosity of the humerus and is inserted into the supraglenoid tubercle of the glenoid cavity. It is held in the bicipital groove by the transverse ligament and a fibrous expansion from the pectoralis major muscle. It acts as a stabilizer of the humeroglenoid joint in abduction.

*Microscopic Anatomy of the Supraspinatus Tendon and Humeral Head.*—The muscle cells run into the tendinous part abruptly. The tendinous portion consists of primary bundles with their rows of fibroblasts grouped into secondary bundles of fibrillar connective tissue. The base of the subacromial bursa and the shoulder joint lie on either side of the tendon and form a bursa for the total depth of the structure of the tendon.<sup>19</sup> The vascular supply runs mostly in the loose septal connective tissue. The vascular supply consists of blood vessels, particularly in adult life. During youth the

T. B.: Movements of the Shoulder Joint: Plea for Use of "Plane of Reference for Movements Occurring at Humero-Scapular Joints, Brit. J. Surg., 1925, 12, 1.

13. Smith, J. F., and Christensen, H. H.: Deltoid Paralysis Followed by Rupture of the Supraspinatus Tendon, *Canad. J. Surg., Gynec. & Obst.* 41:451, 1925.

14. Moseley, H. F.: Rupture of the Supraspinatus Tendon, *Canad. J. Surg., Gynec. & Obst.* 41:451, 1925.

15. (a) Gray, C. H.: Rupture of Supraspinatus Tendon, *Lancet* 1:422, 1925. (c) Wilson.<sup>14</sup>

16. Martin, C. P.: Movements of the Shoulder Joint with Special Reference to the Supraspinatus Tendon, *Am. J. Anat.* 66:213, 1940.

17. Gray.<sup>15</sup> Johnston.<sup>12b</sup>

18. (a) Moseley, H. F.: Shoulder Pain, *Canad. M. A. J.* 46:361, 1942. (c) Moseley.<sup>14</sup> (d) Moseley.<sup>6</sup> Skinner.<sup>9</sup>

vascularized.<sup>19</sup> There are slits seen between the primary collagenous bundles, with a fibroblast seen usually on one side, never on both sides. Sobotta<sup>19c</sup> suggested that these slits contain a cement substance fastening the tendon bundles together. They may serve some such function or may be simply artefacts. There seems to be no reason to assume, as Howard<sup>20</sup> has suggested, that these are all endothelium-lined spaces. He went so far as to state that there are no fibroblasts in tendons and that all the cells are endothelial cells lining spaces for the lubrication of tendons by plasma. His experimental methods are open to several objections, and his observations cannot be regarded as conclusive.

Codman<sup>11</sup> devised a nomenclature of the structures composing the supraspinatus tendon insertion. The tendon is inserted into the greater tuberosity of the humerus through a layer of fibrocartilage which he called "the palisades." The spindle-shaped cells lying in this layer he named "torpedo cells." A thin calcified layer of this fibrocartilage adjacent to the bone is called the "blue line." This line is formed from about 12 to 18 years of age. The cortical bone beneath the blue line is the "armor plate." The "critical portion" of the supraspinatus tendon is the half-inch (1.3 cm.) proximal to the palisades, so named because it is at this point that rupture occurs.

## II. DEGENERATION AND RUPTURE OF THE SUPRASPINATUS TENDON

*Historical.*—The first to recognize a rupture of the supraspinatus tendon was Smith<sup>21</sup> in 1835. Working on anatomic specimens, some of them "snatched from the grave," he described 7 cases of "injuries" of the shoulder in a series of 40 cadavers. The lesions he described were rupture of the supraspinatus tendon with or without rupture of the other short rotator tendons and sometimes rupture of the long head of the biceps with secondary reattachment in the bicipital groove. He attributed these lesions to dislocation of the head of the humerus. It must be noted, however, that in 1788 Alexander Monro<sup>22</sup> in his "Description of all the 'Bursae Mucosae' of the Human Body" published an illustration of "a hole worn in the capsular ligament of the humerus on the right side." It seems that Monro must be given the credit for first describing a ruptured supraspinatus tendon, even if he did not recognize it as such because of the blending of the tendons of the short rotators of the humerus with each other and with the capsule of the shoulder joint. It was not until 1911 that Codman<sup>11</sup> recognized rupture of the supraspinatus tendon as a clinical entity. By means of arduous work and many publications and by his book "The Shoulder" he has succeeded in arousing interest in this and other degenerative lesions making up a very important group of conditions affecting the shoulder joint.

*Pathologic Anatomy.*—Rupture of the supraspinatus tendon occurs as a transverse tear in the fibers of the tendon within a half-inch of the insertion of the tendon into the greater tuberosity of the humerus. The rupture may be partial or complete. Incomplete rupture may occur on the joint side of the tendon where it is called a rim rent, on the bursal side of the tendon involving the floor of the

19. (a) Lindblom, K.: Arthrography and Roentgenography in Ruptures of Tendons of the Shoulder, *Acta radiol.* **20**:548, 1939. (b) Rau, cited by Honigsman, F.: *Med. Klin.* **22**:728, 1926. (c) Sobotta, J.: *Atlas of Human Histology and Microscopic Anatomy*, translated by U. H. Piersol, New York, G. E. Stechert & Company, 1930. (d) Lindblom.<sup>10</sup>

20. Howard, N. J.: Pathological Changes Induced in Tendons Through Trauma and Their Accompanying Clinical Phenomena, *Am. J. Surg.* **51**:689, 1941.

21. Smith, J. S.: Pathological Appearances of Seven Cases of Injury of the Shoulder Joints, with Remarks, *Am. J. M. Sc.* **16**:219, 1835.

22. Monro, A.: *A Description of All the "Bursae Mucosae" of the Human Body*, Edinburgh, C. Elliot, T. Kay & Co., 1788.

subacromial bursa or within the substance of the tendon, involving neither surface.<sup>1h</sup> When a rim rent occurs there is apparent lengthening of the tendon.<sup>7b</sup> If the bursal side is first involved there is furring of the floor of the bursa and later fibrillation of the tendon fibers.<sup>23</sup>

In the majority of cases of complete rupture there is found a defect at the critical portion of the supraspinatus tendon which allows free communication between the shoulder joint and the subacromial bursa. Sometimes the rupture extends to the subscapularis or may even involve the latter alone: sometimes it extends to the insertions of the infraspinatus and teres minor tendons, and sometimes it involves all four tendons, thus completely tearing away the lateral margin of the capsule of the shoulder joint.<sup>1h</sup> In some cases there is blood clot in the early stages and in others none.<sup>24</sup> As the defect of the supraspinatus tendon grows older it becomes triangular,<sup>25</sup> making the rent an equilateral triangle with its base on the greater tuberosity and its apex disappearing under the acromion.<sup>26</sup> The apex becomes falciform and is lined by a rim of hyaline tissue.<sup>1h</sup> Sometimes there is a strap of tendon tissue traversing the rent from apex to base.<sup>27</sup> Meyer cited 1 case in which attrition was carried so far that the deltoid muscle as well as the joint capsule was worn away, leaving only skin and fascia to cover the joint.<sup>28</sup>

In cases of recent rupture a stub of the ruptured tendon is attached to the greater tuberosity of the humerus. This stub is gradually worn away.<sup>29</sup> It has been observed to have disappeared in seventy days.<sup>24a</sup> With rupture of long standing there may be found little bony excrescences on the tuberosity. These are thought to be the result of periosteal reaction to minor repeated traumas. Beneath the cortex there may be seen little absorption caverns.<sup>1h</sup> These may also be seen in normal bones and are supposed to be the result of age.<sup>30</sup> Finally the tuberosity is completely worn away (recession),<sup>31</sup> leaving a smoothly rounded area covered with a thin fibrous layer of periosteum,<sup>1h</sup> which continues the rounded contour of the articular head of the humerus. In cases of long-standing rupture, moreover, the articular cartilage of the head of the humerus is eroded.<sup>32</sup> This erosion is slightly larger than the overlying rent because of movement of the humerus.<sup>33</sup> Eburnation of the receding tuberosity and the overlying acromion may also occur.<sup>34</sup>

Another feature noted in cases of long-standing rupture is that the roof of the subacromial bursa, which normally is filmlike, is as thick as blotting paper.<sup>35</sup>

23. Meyer, A. W.: Further Evidences of Attrition in the Human Body, *Am. J. Anat.* **34**: 241, 1924.

24. (a) Davis, T. W., and Sullivan, J. E.: Rupture of Supraspinatus Tendon, *Ann. Surg.* **106**:1058, 1937. (b) Mayer, L.: Rupture of the Supraspinatus Tendon, *J. Bone & Joint Surg.* **19**:640, 1937.

25. Codman.<sup>1h</sup> Skinner.<sup>9</sup> Wilson.<sup>4a</sup>

26. (a) Keyes, E. L.: Observations on Rupture of Supraspinatus Tendon Based on Study of Seventy-Three Cadavers, *Ann. Surg.* **97**:849, 1933. (b) Codman.<sup>1h</sup>

27. Codman.<sup>1h</sup> Davis and Sullivan.<sup>24a</sup> Keyes.<sup>26</sup>

28. Meyer, A. W.: Chronic Functional Lesions of the Shoulder, *Arch. Surg.* **35**:646 (Oct.) 1937.

29. Codman.<sup>1h</sup> Skinner.<sup>9</sup>

30. Meyer, A. W.: Unrecognized Occupational Destruction of the Tendon of the Long Head of the Biceps Brachii, *Arch. Surg.* **2**:130 (Jan.) 1921.

31. (a) Horwitz, M. T.: Lesions of the Supraspinatus Tendon and Associated Structures: Investigation of Comparable Lesions in Hip-Joint, *Arch. Surg.* **38**:990 (June) 1939. (b) Codman.<sup>1h</sup> (c) Skinner.<sup>9</sup>

32. Codman.<sup>1h</sup> Meyer.<sup>30</sup> Skinner.<sup>9</sup>

33. Keyes, E. L.: Cadaver Observations: Anatomical Observations on Senile Changes in the Shoulder, *J. Bone & Joint Surg.* **17**:953, 1935. Codman.<sup>1h</sup>

34. Codman.<sup>1h</sup> Meyer.<sup>23</sup> Meyer.<sup>28</sup> Meyer.<sup>30</sup>

35. Codman.<sup>1h</sup> Horwitz.<sup>31</sup>

Synovial villi may be found in the bursa.<sup>36</sup> At operation they are pink, but at autopsy they are limp and colorless. Sometimes thick fibrous bands are found in the bursa.<sup>37</sup> The subacromial bursa may be absent, there being only a loose areolar tissue binding the internal surface of the deltoid to the joint capsule.<sup>23</sup> Roughening, fraying and complete destruction of the synovial bursae may result from long-continued wear,<sup>28</sup> from rupture of the supraspinatus tendon<sup>38</sup> or from a deposit of calcium in the supraspinatus tendon which has ruptured into the bursa.

The tendon of the long head of the biceps muscle is exposed as it passes over the head of the humerus by a rent in the supraspinatus tendon.<sup>39</sup> It is seen as a bright pink<sup>11</sup> or frayed<sup>20</sup> band crossing the articular cartilage of the humeral head and may sometimes be twice as wide as its natural diameter. In cases of long-standing rupture of the supraspinatus tendon the intra-articular portion of the biceps tendon is absent. The attachment at the supraglenoid tubercle has been lost and the tendon has become reattached in the bicipital groove or to the transverse humeral ligament.<sup>40</sup> The intracapsular portion may disappear completely or may fuse with the joint capsule.<sup>30</sup> It has also been described as being attached to the articular surface of the head of the humerus like a ligamentum teres.<sup>31a</sup> Meyer<sup>28</sup> took great pains to point out that rupture of the biceps tendon occasionally (3 cases) may occur with an intact shoulder capsule, and he attributes this to attrition. His 3 patients had roughening of the head of the humerus. Other causes of rupture of the biceps tendon were adequately discussed by Gilcreest,<sup>30a</sup> but they must be rare.<sup>7b</sup>

Characteristic histologic changes are found in the degenerating but intact supraspinatus tendon.<sup>7b</sup> The tendon bundles lose their wavy appearance and become at first granular, later clear and homogeneous and finally fibrillar. There is an increase in the number of arterioles, and they can be seen growing down from the base of the subacromial bursa and occasionally up from the joint capsule. With hematoxylin and eosin, normal tendon bundles stain a deep pink. The more degenerate a tendon is, the paler pink it will stain. Mallory's connective tissue stain colors the normal tendon bundles orange and the degenerative areas blue. The most marked changes of this character are found in ruptured tendons at the site of rupture. It is evident that the degenerative process described leads to weakening of the tendon of such a degree that eventually rupture of the tendon under relatively slight strain becomes possible.<sup>7b</sup> It has been stated<sup>41</sup> that degenerated areas stain a deeper pink with eosin, but in my series this has not held true.<sup>7b</sup> It is almost impossible to find a histologically normal supraspinatus tendon in an old person.<sup>11</sup>

At the insertion the torpedo cells may become calcified, may form peculiar giant cells or may fade. The palisades often stain irregularly, indicating necrotic changes. The blue line may be pushed up by excrescences or torn out in patches by the tendons. The armor plate may be at first thickened and later thinned in a receding tuberosity.<sup>11</sup> There is a thin layer of fibrous tissue covering the bony cortex of the receding tuberosity. Beneath the excrescences are often found caverns con-

36. Codman.<sup>11</sup> Meyer.<sup>30</sup>

37. Ferguson, L. K.: Painful Shoulder Arising from Lesions of Subacromial Bursa and Supraspinatus Tendon, *Ann. Surg.* **105**:243, 1937. Codman.<sup>11</sup>

38. Akerson, I. B., and Codman, E. A.: Pathology Associated with Rupture of the Supraspinatus Tendon, *Ann. Surg.* **93**:348, 1931.

39. (a) Gilcreest, E. L.: The Common Syndrome of Rupture: Dislocation and Elongation of the Long Head of the Biceps Brachii; Analysis of One Hundred Cases, *Surg., Gynec. & Obst.* **58**:322, 1934. (b) Wilson, P. D.: The Painful Shoulder, *Brit. M. J.* **2**:1261, 1939. (c) Codman.<sup>11</sup> (d) Meyer.<sup>30</sup> (e) Smith.<sup>21</sup> (f) Wilson.<sup>4a</sup>

40. Codman.<sup>11</sup> Horwitz.<sup>31</sup> Meyer (footnotes 23, 28 and 30). Skinner.<sup>9</sup>

41. Codman.<sup>11</sup> Lindblom (footnotes 10 and 19 a).

taining vascular tissue. In a late stage, when the tuberosity is receding, the blue line tends to disappear. The armor plate may be thickened following rupture but is thin in recession of the tuberosity.<sup>41</sup> In the subacromial bursa there are vascular and cellular villi which project into the bursa,<sup>42</sup> and in a late stage the walls of the bursa are thickened.

*Tensile Strength.*—Cronkite,<sup>43</sup> using tendon strips from various tendons with a cross-sectional area of approximately 0.5 to 1 sq. mm., tested the breaking strength and found variations from 4,000 to 30,000 pounds per square inch (2.8 to 21 Kg. per square millimeter) for individual tendons. The average breaking strength of the tendons of different cadavers varied from 8,700 to 18,000 pounds per square inch (6 to 12.5 Kg. per square millimeter). The tensile strength of fresh tendon did not in his estimation differ much from that of tendon fixed with glycerin and alcohol. The strength of the tendons appeared to have no relationship to the assigned cause of death or to the age of the patient. He estimated that a pull of 1,000 pounds (454 Kg.) would be required to rupture a normal supraspinatus tendon 3 mm. thick and 2 cm. wide.

McMaster<sup>44</sup> made preparations of rabbit's gastrocnemius muscle, intact with its tendon and bones of origin and insertion. He subjected the system to strain by pulling the two bones apart in the direction of normal muscle pull. The break in a normal preparation occurred anywhere but in the tendon. The closest approach to a break in the tendon occurred when it pulled away from the calcaneus, carrying a fragment of bone with it. Approximately one half of the tendon's fibers had to be severed to permit rupture of the tendon when the system was subjected to strain. Spontaneous rupture did not occur after severance of three fourths of a tendon's fibers under ordinary activities of a rabbit. This proved that the tendon is the strongest link in this particular muscle to bone chain in the rabbit. Obstruction of the blood supply of 1 cm. of a normal tendon by double ligation caused rupture at the obstructed area, but only when it was subjected to strain four to five weeks later. When tests were made earlier than this the break occurred not in the tendon but elsewhere in the system. The blood supply of a tendon was found to be more important in reparative processes of injured tendons than the presence of a tendon sheath.

Lindblom<sup>45</sup> experimented with preparations of humerus, supraspinatus tendon and muscle with sutures placed in the latter to act as a grip. By exerting a sudden force of 4 to 11 Kg. he was able to produce rupture of the tendon at its insertion in 2 cases out of 7. His conclusion was that the direction of force was important, but since the only persons in which he was able to produce experimental rupture of the supraspinatus tendon were over 70 years of age it would seem, in view of my work,<sup>7b</sup> that these tendons were probably in at least a slightly degenerated state. In younger persons Lindblom did not succeed in producing a rupture in the tendinous portion of the system. In my small series<sup>7b</sup> rupture occurred anywhere but in the tendinous portion of a bone-muscle-tendon-bone preparation of the supraspinatus muscle. The conclusion is that rupture of a normal tendon does not occur and that prior degenerative changes with weakening of the tendon are essential to its rupture by force.

*Incidence.*—The figures of incidence of complete rupture of the supraspinatus tendon have varied with different authors according to the type and age of the

42. Codman,<sup>1h</sup> Howard.<sup>20</sup>

43. Cronkite, A. E.: Tensile Strength of Human Tendons. *Anat. Rec.* 64:173, 1936.

44. McMaster, P. E.: Tendon and Muscle Ruptures: Clinical and Experimental Studies on the Causes and Location of Subcutaneous Ruptures. *J. Bone & Joint Surg.* 15:705, 1933.

45. Lindblom (footnotes 10 and 19 a).

subjects with which they were working. Statistics generally have been given as a percentage of the number of shoulders examined (i. e., two shoulders per subject). Codman,<sup>11</sup> working on autopsy and surgical material, estimated that the incidence on this basis was at least 5 per cent. Akerson,<sup>38</sup> doing autopsies on old, debilitated people, found it to be 39 per cent. In Skinner's series<sup>9</sup> it was 6 per cent and in Keyes' series 13 per cent.<sup>26a</sup> My own statistics<sup>7b</sup> were quoted as a percentage of the bodies examined, since each case, in a clinical sense, means 1 patient and this is what is important, not whether the rupture is unilateral or bilateral. In autopsy material the incidence was 20 per cent and in anatomic cadavers 26.5 per cent. In about half the cases rupture was bilateral. The average age of the autopsy subjects was 55 years and of the cadavers was 66, but in both groups the average age of those with ruptured tendons was virtually the same. All authors have agreed that the average age of subjects with rupture is in the neighborhood of 64 years.<sup>46</sup> Rupture occurs much more frequently in males than in females, the incidence in my series being 23.7 per cent among males and 17.8 per cent among females.<sup>7b</sup> The incidence is much higher on the right side than on the left,<sup>47</sup> although in one series this was not true.<sup>26a</sup> In my series<sup>7b</sup> no rupture occurred on the left side without a larger one on the right. All unilateral ruptures occurred on the right side except in 2 instances. These were the only cases in the series in which the circumference of the left arm at the level of the biceps exceeded that on the right.

*Etiology and Pathogenesis.*—Much has been written concerning the cause of rupture of the supraspinatus tendon. Certain general hypotheses are admitted by every one, but no definite proofs have been established. There has been more theorizing than definite data on this subject. Every one agrees that ruptures do not usually occur in persons under the age of 50 years. Actual figures based on the examination of at least 500 bodies bear this out.<sup>48</sup> The youngest patient on record was a woman only 32 years of age.<sup>49</sup> In the younger age groups, instead of rupture of the tendon, fracture of the greater tuberosity occurs. Many authors have speculated that changes occur in the structure of the tendon with age, but the ideas concerning these changes vary, some authors having merely postulated a senile degeneration and gone no further.<sup>50</sup> It has been suggested that degeneration may be due to deterioration of the vascular supply.<sup>51</sup> The supposed change has also been called a sclerosization.<sup>45</sup> Wilson and Duff<sup>7b</sup> have shown that characteristic microscopic degenerative changes make their first appearance relatively early in adult life and increase with age.

Most surgeons are of the opinion that rupture usually occurs in a tendon which has suffered degeneration and then been subjected to trauma.<sup>52</sup> There are divergent opinions as to the nature of this trauma. Most authors believe that the trauma is the result of muscular violence. Smith<sup>21</sup> in his original article expressed the opinion that dislocation of the head of the humerus was the cause, and Outland and Shepherd<sup>53</sup> reported 3 cases in which such dislocation was responsible. It has been pointed out that when external rotation of the humerus

46. Keyes.<sup>26a</sup> Wilson.<sup>7b</sup>

47. Akerson.<sup>38</sup> Lindblom.<sup>10</sup> Wilson.<sup>7b</sup>

48. Codman.<sup>11</sup> Keyes.<sup>26a</sup> Keyes.<sup>33</sup> Lindblom.<sup>45</sup> Wilson.<sup>7b</sup>

49. (a) Fowler, E. B.: Stiff and Painful Shoulders Exclusive of Tuberculosis and Other Infections, J. A. M. A. **101**:2106 (Dec. 20) 1933. (b) Thompson, C. E., and McLaughlin, C. W., Jr.: Calcified Deposits in Subscapularis Tendon, Am. J. Surg. **32**:524, 1936.

50. Davis and Sullivan.<sup>24a</sup> Gray.<sup>15a</sup> Horwitz.<sup>31a</sup>

51. (a) Codman.<sup>11h,1</sup> (b) Wilson.<sup>4a</sup>

52. Codman.<sup>11h,1</sup> Gray.<sup>15a</sup> Horwitz.<sup>31a</sup> Keyes.<sup>26a</sup> Lindblom.<sup>45</sup> Skinner.<sup>9</sup> Wilson.<sup>4a</sup>

53. Outland, T. A., and Shepherd, W. F.: Tears of the Supraspinatus Tendon: Résumé of Twelve Operated Cases, Ann. Surg. **107**:116, 1938.

is prevented during abduction, the coracoacromial arch bears sharply on the insertion of the supraspinatus tendon and may lacerate it.<sup>16</sup> A traumatic condition simulating rupture may occur in a healthy tendon. This has been well illustrated by Codman,<sup>1b</sup> in whose book there is a plate showing a tendon in which the torn end contains a fragment of bone. That this is a traumatic fracture of the greater tuberosity rather than of the tendon is in agreement with experimental results.<sup>54</sup> Howard<sup>20</sup> presented the idea that trauma may cause a vascular granulation tissue reaction which erodes and frays the tendon so that it eventually ruptures under stress. This suggestion was based on his study of the extensor tendons of the finger.

It has also been suggested<sup>55</sup> that rupture is due to wear, caused by long-continued use of the arm in abduction with friction against the coracoacromial arch. Codman described ruptures on the under surface of the tendon and pointed out that these could not very well be due to friction against the acromion.<sup>1b</sup> Meyer granted this but pointed out that complete capsular defects may occur anteriorly and posteriorly to the intact supraspinatus tendon<sup>55</sup> and argued that they cannot be due to trauma but must be due to wear,<sup>28</sup> since some of them are parallel to the tendon fibers instead of transverse as would be the case in traumatic rupture.

Various authors<sup>56</sup> have emphasized the importance of occupation. Most of them cite as the cause of rupture of the supraspinatus tendon occupations which require long-continued use of the arm in a position of abduction, especially doing heavy labor. Codman<sup>1</sup> stated that he had encountered only 1 case of rupture in a person whose occupation did not require or had not required heavy work. Whether occupation causes ischemia, due to compression of the vascular supply,<sup>57</sup> or attrition, because of friction,<sup>58</sup> is still problematic. In my series<sup>7b</sup> the histologic changes of degeneration were greater in laboring people.

Todd and Cohen<sup>58</sup> have found in guinea pigs deprived of vitamin C such weakening of the ligaments that it was difficult to skin the animals without tearing the ligaments of the joints, especially of the knee and cervical vertebrae. It seems doubtful, however, that deficiency of vitamin C could be of great importance in patients showing no other signs of vitamin deficiency.

*Clinical Features.*—The first clear description of the clinical features in the acute stage of complete rupture of the supraspinatus tendon was given by Codman.<sup>1b</sup> Usually there have been no symptoms in the shoulder prior to the acute disability, which starts with an injury, usually a fall, in which there is sudden elevation of the arm in an attempt to regain balance. The patient will usually say that he fell and struck his shoulder. This may very rarely be true, but usually it is not, and even if the patient did fall on his shoulder he could not have injured the supraspinatus tendon in falling, since it is protected by the acromion process. After the fall, immediate, sharp, brief pain is always felt in the shoulder at the insertion of the supraspinatus muscle. It may be mild or moderately severe, but is usually not severe enough to prevent the patient from working for the remainder of the day. In the evening the pain becomes worse and later in the night intolerable. The patient calls a doctor, or sits up in a chair or walks the floor. All these features are present within twenty-four hours after the injury. Next day he is

54. McMaster,<sup>44</sup> Wilson.<sup>7b</sup>

55. Meyer, footnotes 23, 28 and 30.

56. Codman.<sup>1b,1</sup> Davis and Sullivan.<sup>24a</sup> Keyes.<sup>26a</sup> Meyer.<sup>55</sup> Skinner.<sup>9</sup>

57. Codman.<sup>1b,1</sup>

58. Todd, T. W., and Cohen, M. B., cited by Todd, T. W.: *Skeleton and Locomotor System*, in Cowdry, E. V.: *Problems of Aging*, Baltimore, Williams & Wilkins Company, 1939, p. 323.



pretty sure to report that he cannot work but may persuade an accommodating foreman to let him "hang around for a day or two" until he gets better, because he usually thinks that the injury is of no great consequence and will wear off. Physical examination reveals an inability to raise the arm. There is little restriction of movement of the shoulder when the patient is leaning forward from the hips with the arms hanging down. This is really a modification of Dawbarn's sign,<sup>59</sup> i. e., disappearance of pain when the arm is abducted because the ruptured tendon has slipped up under the coracoacromial arch where it is protected. A tender point can be felt just anterior to the edge of the tip of the acromion process when the arm is in dorsal flexion. This point is at the gap between the torn ends of the tendon. As the arm is passively elevated this tender point disappears under the coracoacromial arch and the patient experiences a sense of relief. Sometimes this gap can be felt as a sulcus by the examining finger if the intervening deltoid muscle is not too thick. This sulcus accentuates the prominence of the greater tuberosity. The passage of the sulcus in the ruptured tendon under the coracoacromial arch causes a wince of pain, and a jog which is noticeable to the patient and sometimes even to the examiner. When the symptoms and signs are definite and typical and the sulcus is plainly palpable, there should be no doubt of complete rupture but in cases of partial rupture each symptom may be milder and each sign somewhat more doubtful than in the cases of complete rupture. The doubtful character of the findings combined with the presence of a considerable amount of power to hold the arm in the scarecrow position (right-angled abduction) rules out a complete rupture.

During the first few nights following a complete rupture the pain is very severe; then it becomes a nagging pain, bearable but very annoying. This pain is felt near the insertion of the deltoid. It continues without change for months and is aggravated by attempts to work.<sup>1h</sup> The spinatus muscles begin to atrophy after about three weeks.<sup>1h</sup> Unless operated on, the patient never completely recovers the use of his arm. Codman stated that some courageous men persist in working and become free of symptoms in two to five years.<sup>1h</sup> In a late stage there is no tender point, jog or wince. Because of the relatively large number of ruptures found at autopsy, Keyes<sup>26a</sup> doubted that all of them cause symptoms:

Partial rupture may cause pain and disability for a short period and then become symptomless or may go on to adhesions and a "frozen shoulder."<sup>37</sup> In the latter condition slight abduction is painless but cannot be carried beyond this point. This is part of the so-called "subacromial bursitis."

Rupture of the long head of the biceps tendon is one end result of complete rupture of the supraspinatus tendon.<sup>60</sup> When rupture occurs the symptoms are variable.<sup>39a</sup> There may be pain, a sudden, loud perceptible snap or both, or only weakness of the arm. Objectively there may be a bulge of contracted biceps muscle, depending on whether or not secondary reattachment of the tendon has previously occurred in the bicipital groove. A partially torn biceps tendon may give rise to more pain through irritating its sheath by friction than does a completely ruptured tendon.<sup>39a</sup> This point is illustrated in a case described by Moseley<sup>14</sup> of a man with a complete rupture of the supraspinatus tendon which was operated on. Ten years previously he had "the same injury" to the other shoulder, which remained painful for two years until one day he felt a sudden snap in the shoulder and

59. Dawbarn, R. H. M.: Subdeltoid Bursitis: A Pathognomonic Sign for Its Recognition, *Boston M. & S. J.* 154:691, 1906.

60. (a) McKee, G. K.: Spontaneous Rupture of the Long Head of the Biceps, *Brit. M. J.* 1:1018, 1940. (b) Meyer.<sup>30</sup> (c) Moseley.<sup>14</sup>

noted a swelling of his biceps muscle, after which his shoulder was free of pain. The tendon may be displaced instead of ruptured if the lesser tuberosity is worn away.<sup>30</sup>

The rupture of the tendon of the long head of the biceps muscle is most often caused by friction resulting from a capsular defect,<sup>61</sup> i. e., a rupture of the supraspinatus tendon and erosion of the articular cartilage of the head of the humerus.<sup>39b</sup> Secondary reattachment of the ruptured tendon to the bicipital groove or the transverse humeral ligament usually occurs before complete severance of the biceps tendon, because some of the severed and reattached tendons are of the same length as normal tendons.<sup>62</sup> Sometimes, however, rupture occurs before the secondary reattachment, and the tendon is longer than normal and hence functionally useless.

There are two roentgenographic methods for determining whether a supraspinatus tendon is ruptured. Henry<sup>63</sup> employed soft tissue roentgenographic technic using anteroposterior views with the arm in adduction and internal rotation. Immediately after the injury, fine spicules of bone may be seen near or on the periosteal outlines of the greater tuberosity at the site of insertion of the supraspinatus tendon in those cases in which the tendon has been torn off the greater tuberosity.<sup>63</sup> Usually, however, the rupture occurs at the critical portion of the tendon, and in these cases the roentgenogram appears normal. The humeral head is held high in the glenoid cavity.<sup>18a</sup> Within several weeks after the injury the density of the bone of the greater tuberosity varies from the normal; atrophy of the trabeculae or irregular roughening about the sulcus occurs<sup>63</sup> (osteitis of Codman).<sup>1b</sup> Within six months to one year there are found rounding off and loss of the greater tuberosity, irregular calcification and occasionally cysts in the cortical bone of the head of the humerus. Older lesions may also show thickening of the cortex (eburnation of Codman) and rearrangement of the trabeculae.<sup>63</sup>

Lindblom<sup>19a</sup> introduced the method of injecting a solution of 6 cc. of a 35 per cent solution of diodrast mixed with 1 cc. of 1 per cent procaine hydrochloride solution into the shoulder joint 1 cm. anterolateral to the coracoacromial joint, in the direction of the center of the head of the humerus. The arm is moved passively to spread the contrast medium, and roentgenograms are taken immediately, because the solution is rapidly absorbed. Normally the contrast medium fills the cavity of the joint, the tendon sheath of the biceps and the bursa of the subscapularis muscle. No other communications exist in the normal joint except an occasional communication with a bursa very rarely found under the infraspinatus tendon.<sup>3a</sup> In cases of rupture of the supraspinatus tendon, either a finger-like projection flows out of the joint cavity or else a free communication exists between the joint and the subacromial bursa.

*Treatment.*—Credit for the present knowledge of the treatment of complete rupture of the supraspinatus tendon must go to Codman. The treatment is operative repair, and the best time is immediately after the injury.<sup>64</sup> When the diagnosis was doubtful Codman advised exploratory incision of the bursa with local anesthesia.

61. McKee.<sup>60a</sup> Meyer.<sup>50</sup> Wilson.<sup>39b</sup>

62. Meyer (footnotes 28 and 30).

63. Henry, L. S.: Roentgenographic Evidence in the Tuberosity of the Humerus of Recent and Old Injuries to the Supraspinatus Tendon Attachment, *Am. J. Roentgenol.* **33**:486, 1935.

64. Brumbaugh, H. L.: (a) Rupture of Supraspinatus: Diagnosis and Treatment of Post-Traumatic Changes in and About Joints, *Ohio State M. J.* **35**:597, 1939; (b) Calcifying Tendinitis Traumatica, *Am. J. Surg.* **48**:681, 1940. (c) De Courcy, J. L.: Rupture of Muscles and Tendons, *Am. J. Surg.* **36**:283, 1937. (d) Codman.<sup>1d, f, g, h, i</sup> (e) Davis.<sup>24a</sup> (f) Gray.<sup>15a</sup> Laird.<sup>5</sup> McKeown.<sup>7a</sup> Moseley.<sup>14</sup> Moseley.<sup>6</sup> Moseley.<sup>15a</sup> Wilson.<sup>4a</sup> Wilson.<sup>39b</sup>

The position of the patient during operation is important.<sup>1b</sup> The requirements are that the shoulder must be held steady yet the position must permit mobilization of the arm to allow all the short rotator tendons of the shoulder to be visualized through the small operative incision, as the arm is rotated. Codman's position fulfils these requirements. A heavy sandbag is placed under the affected shoulder and another under the hip on the same side, thus turning the patient partly on his side with the head and neck falling away from the operative field. The patient is placed with the affected shoulder at the side of the table, so that the affected arm hangs over the edge to permit its rotation by an assistant. The whole arm is draped so that it can be handled.

A vertical incision  $1\frac{1}{2}$  inches (3.8 cm.) long is made over the anterior aspect of the head of the humerus with its upper end near the acromioclavicular joint and its lower end at the top of the bicipital groove.<sup>1b</sup> The latter point is the most anterior prominence when the forearm is flexed to a right angle to the arm and placed at a right angle to the table. This position is important too for incising the bursa, because if the arm is not in this position it is liable to be internally rotated, and then the incision will miss the bursa completely. After the skin and muscle are incised hemostasis should be secured before the bursa is entered. The latter is opened by a method similar to that employed for opening the peritoneum, i. e. by incision between two forceps.

When the bursa has been opened, the arm is rotated to visualize all of the base of the bursa, and the degree of rupture is then easily ascertained. In an early stage (i. e., within two weeks<sup>24a</sup>) repair is easy. In a late stage, in which retraction of the tendon has occurred, it is difficult. The tendon should be mobilized as much as possible and then pulled down. Injury to the suprascapular nerve as it winds around the lateral border of the spine of the scapula must be avoided. Sutures will tear out of the hyaline edge of the falciform border of an old defect; so this edge must be pared away before repair is attempted. If the long head of the biceps tendon is roughened and not capable of forming a smooth cord, it should be divided and the lower end attached to the bicipital groove and the upper portion attached to the supraspinatus tendon so as to help fill the gap. If the biceps tendon is intact it should be left alone, so that its function of stabilizing the shoulder may remain. The other functions of the biceps tendon are maintained when the long head has been sutured to the bicipital groove.

Heavy silk is probably the best material to use for repair of the defect in the tendon,<sup>1</sup> but fascia lata has also been employed. If there is no stub of tendon on the greater tuberosity capable of holding sutures, holes should be bored in the greater tuberosity, through which the heavy silk sutures may be passed. Soon after the rupture the closure of the defect is simple; in a later stage, when there is retraction of the tendon it may be necessary also to close the defect from side to side. To give the tendon a surface to adhere to, the tuberosity should be roughened,<sup>1b</sup> or even a little slot cut as a new sulcus to which the tendon is held.<sup>65</sup> The roof of the subacromial bursa should be left open to permit the escape of fluid which if confined would cause pain.<sup>1b</sup> Very rarely persistent pain after the operation may be due to reaction of the tissues about the silk sutures. This can be relieved by opening the bursa with local anesthesia and removing the sutures.

The saber cut incision dividing the acromion, while giving a better exposure, converts a minor into a major surgical operation,<sup>1b</sup> and Codman abandoned it. It may be useful in cases of old rupture when the surgeon requires a greater exposure. P. D. Wilson makes the  $1\frac{1}{2}$  inch (3.8 cm.) anterior incision, and if

65. Wilson.<sup>4a</sup> Wilson.<sup>39b</sup>

the rupture is found to be very large he then makes the saber cut incision.<sup>1a</sup> Codman found that with an able assistant to rotate the arm adequate exposure was supplied by the small anterior incision through the deltoid muscle. There is little to support Mayer's contention<sup>24b</sup> that this incision weakens the fibers of the deltoid muscle anterior to the incision unless, of course, one cuts so low as to divide the circumflex nerve.

Regarding the problem of postoperative treatment, there are advocates of both abduction and adduction positions. Codman<sup>1</sup> recommended a pad in the axilla and a small pillow for the arm and forearm to prevent too much internal rotation. After the first night the patient is allowed to assume any position which he finds comfortable. The patient is given gradually increasing exercise, at first using passive movement by bending at the hips and letting the arms hang down, so that by the end of a week he can bend the hips to a right angle. By gently twisting and rolling the shoulder he can move it passively. During the second week he should start swinging the arms actively in the bent-over position. He may be discharged in ten to fourteen days to continue the stooping exercises until he can abduct the arm freely and then should start abduction in the erect position. Others have advised immobilization in 60 degrees of abduction for two or three weeks after operation<sup>66</sup> and even in 120 degrees for four weeks.<sup>24b</sup> This procedure causes an abduction contracture, which, however, will yield in several weeks.<sup>24b</sup> If any one elects to use abduction he should be certain to remember that the abducted arm should be slightly anterior to the coronal plane of the body, i. e., in the plane of the scapula.

One method of treatment of partial rupture is to maintain a complete range of movement from the beginning.<sup>67</sup> In the early treatment injection of procaine hydrochloride into the most tender spot relieves the pain, and the movements can then be carried out.<sup>18a</sup> Short wave diathermy is also of use.<sup>68</sup> The other method of treatment is by immobilization, application of heat and gradually increasing exercises within the limit of pain.<sup>37</sup> Operation offers these patients nothing.<sup>1b</sup>

If there is rupture of the tendon of the long head of the biceps associated with an old complete rupture of the supraspinatus tendon, nothing can be done for the latter at this late stage, but the biceps tendon should be sutured to the bicipital groove or to the short head of the biceps muscle, the coracoid process or both.<sup>69</sup> For slight tears of the biceps tendon the arm may be immobilized without operation in acute flexion for two or three weeks. It is then gradually lowered and physical therapy started. This method reduces the muscular power of the biceps by about 30 per cent, and the cosmetic effect is poor.<sup>60a</sup> McKee<sup>60a</sup> makes the incision for repair of a rupture of the supraspinatus tendon also a lower one, over the biceps tendon, below the insertion of the pectoralis major muscle. He threads the tendon back through its groove and sutures it in the intertubercular sulcus below the notch.

### III. CALCIFICATION OF THE SUPRASPINATUS TENDON

*Historical Aspects.*—Painter in 1905<sup>70</sup> was the first to recognize calcium deposits in roentgenograms of the shoulder. He thought the shadows he observed were due to thickening of the subdeltoid bursa. But Codman, who was present

66. Davis and Sullivan.<sup>24a</sup> Moseley.<sup>6</sup>

67. Codman.<sup>1b</sup> Moseley.<sup>6</sup> Moseley.<sup>14</sup> Moseley.<sup>18a</sup>

68. Moseley (footnotes 6, 14 and 18a).

69. Bishop, W. A., Jr.: Calcification of the Supraspinatus Tendon: Cause, Pathologic Picture and Relation to Scalenus Anticus Syndrome. *Arch. Surg.* 39:231 (Aug.) 1939.

70. Painter, C. F.: Subdeltoid Bursitis. *Boston M. & S. J.* 156:345, 1907.

at one of Painter's operations, was the first to realize that the deposit was actually in the supraspinatus tendon.

*Pathologic Anatomy.*—Gross: Calcium is deposited in the short tendons of the shoulder capsule,<sup>71</sup> most frequently in the supraspinatus tendon.<sup>72</sup> On the base of the subacromial bursa in the tendon involved there is an elevation with a grayish white center and a red turgid periphery, resembling a boil.<sup>73</sup> The bursa contains a fibrinous exudate. The calcium deposit at this stage is soft and creamy<sup>74</sup> and resembles staphylococcic pus or may be firmer and of the consistency of toothpaste. The areas of deposit are frequently multiloculated.<sup>75a</sup> The acute symptoms are caused by involvement of the base of the subacromial bursa.<sup>75</sup> The calcium deposit may rupture into the subacromial bursa, producing a chemical bursitis,<sup>76</sup> and the site of rupture may often be demonstrated at operation.<sup>77</sup>

In the subacute and chronic phases there is usually little abnormality to be seen in the bursa. The deposit may have to be located by feeling a swelling.<sup>78</sup> The deposit is usually cheesy or gritty.<sup>79</sup> In some cases it will shell out easily, but in others it is embedded among the fibers of the tendon,<sup>80</sup> requiring curettage.

*Microscopic:* Calcium deposits may occur as a number of foci of varying size embedded in a tendon which shows fibrosis and is infiltrated with masses of chronic inflammatory cells, mostly lymphocytes and plasma cells with a few giant cells. The connective tissue may show hyalinization.<sup>81</sup> In a case I studied recently the tendon contained many polymorphonuclear leukocytes as well as small round cells and giant cells.

*Chemical Composition of the Deposits.*—Calcium has been reported as occurring in the form of calcium carbonate and calcium phosphate ( $\text{Ca}_3[\text{PO}_4]_2$ ),<sup>82</sup> and some analyses show calcium oxalate.<sup>83</sup> The analyses have differed greatly as to the proportion in which these calcium salts occur.

*Incidence.*—The only reliable figures of incidence are those of Bosworth.<sup>71a</sup> Among 6,061 supposedly normal persons of the "white collar" class, calcium was found on routine fluoroscopic examination in 165 (2.7 per cent) in one or both shoulders. The lesion was found most frequently in the period of greatest activity

71. (a) Bosworth, B. M.: Calcium Deposits in Shoulder and Subacromial Bursitis: A Survey of 12,122 Shoulders, *J. A. M. A.* **116**:2477 (May 31) 1941. (b) Brickner, W. M.: Prevalent Fallacies Concerning Subacromial Bursitis: Its Pathogenesis and Rational Operative Treatment, *Am. J. M. Sc.* **149**:351, 1915. (c) Carnett, J. B.: Calcareous Deposits of the So-Called Subacromial Bursitis, *Surg., Gynec. & Obst.* **41**:404, 1925. (d) Emslie, R. C.: Calcareous Deposits in the Supraspinatus Tendon, *Brit. J. Surg.* **20**:190, 1932. (e) Fahey, J. J., and Harmon, P. H.: Calcification of Posterior Portion of the Greater Tubercle of the Humerus: Differentiation from Supraspinatus Tendon Calcification, *Am. J. Roentgenol.* **38**:707, 1937. (f) Rogers, M. H.: Treatment of Subdeltoid Bursitis, *Am. J. Surg.* **43**:292, 1939. (g) Wardle, E. N.: Calcification in Supraspinatus Tendon, *J. Bone & Joint Surg.* **17**:789, 1935. (h) Codman.<sup>1h</sup> (i) Wilson.<sup>4a</sup> (j) Wilson.<sup>39b</sup>

72. Bishop.<sup>69</sup> Bosworth.<sup>71a</sup> Codman.<sup>1h</sup>

73. Codman.<sup>1h</sup> Emslie.<sup>71d</sup>

74. Codman.<sup>1h</sup> Rogers.<sup>71f</sup>

75. Codman.<sup>1h</sup> Wilson.<sup>39b</sup>

76. Bishop.<sup>69</sup> Codman.<sup>1h</sup> Moseley.<sup>18a</sup> Wilson.<sup>39b</sup>

77. Brickner.<sup>71b</sup> Wilson.<sup>39b</sup>

78. Codman.<sup>1h</sup> Emslie.<sup>71d</sup>

79. Codman.<sup>1h</sup> Moseley.<sup>18a</sup> Rogers.<sup>71f</sup>

80. Brickner.<sup>71b</sup> Codman.<sup>1h</sup> Rogers.<sup>71f</sup>

81. (a) Moschowitz, E.: Histopathology of Calcification of the Supraspinatus Tendon <sup>as</sup> Associated with Subacromial Bursitis, *Am. J. M. Sc.* **150**:115, 1915. (b) Bishop.<sup>69</sup> (c) Codman.<sup>1h</sup> (d) Emslie.<sup>71d</sup>

82. Bishop.<sup>69</sup> Brickner.<sup>71b</sup> Emslie.<sup>71d</sup> Moseley.<sup>18a</sup> Painter.<sup>70</sup> Rogers.<sup>71f</sup> Wilson.<sup>39b</sup>

83. Bishop.<sup>69</sup> Brickner.<sup>71b</sup>

of adult life, nearly all of his subjects being under 50 years of age. This has been corroborated by other authors.<sup>84</sup> It occurs more often in males.<sup>85</sup> Among 1,178 males in Bosworth's series,<sup>71a</sup> the incidence of calcification was 3.6 per cent, while among 3,883 females the incidence was only 2.5 per cent.

*Etiology and Pathogenesis.*—Occupation: Women typists have a significantly higher incidence of calcium deposits than women clerks throughout all age groups.<sup>71a</sup> "Millions of years of heredity have not yet prepared the modern stenographer or machine operator to keep their supraspinatus tendons stretched and under tension, on the qui vive, hour after hour, day after day."<sup>1b</sup> That is to say, long-continued use of the arm in abduction seems to be a predisposing factor.

Trauma: A single severe trauma does not cause calcification but may precipitate acute symptoms in an already existing deposit.<sup>86</sup> Many patients have had known calcium deposits in one or both shoulders for months or years prior to an acute attack,<sup>87</sup> and many patients experience a severe attack with no history of trauma.<sup>88</sup> Many authors have expressed the opinion that minor, often repeated traumas cause necrosis and/or hyalinization due to poor blood supply and that calcification subsequently occurs.<sup>89</sup> This last would seem to be the most likely cause of calcification. A later trauma probably initiates the clinical syndrome.

Infection seems to play no part in the formation of calcium deposits.<sup>90</sup> Many have operated on these deposits and made bacteriologic cultures which have given negative results.<sup>91</sup> Brickner<sup>71b</sup> reported 3 positive results of cultures and Codman and Harrington<sup>1b</sup> 1 culture that yielded *Staphylococcus aureus*. It was later admitted that the last one was probably contaminated.<sup>1b</sup> Dickson and Crosby<sup>92</sup> expressed the belief that an infectious or toxic focus anywhere in the body may aid in precipitating an attack, but others with wide experience have not agreed with this view.<sup>93</sup> To explain why calcification occurs, Wells's<sup>94</sup> theory of calcification has been invoked.<sup>69</sup> It presupposes the presence of a necrotic area. In such an area no oxidation occurs. Consequently no carbon dioxide is produced and the medium becomes alkaline, causing precipitation of calcium. Calcium values in the blood of persons with large deposits of calcium in the supraspinatus tendon, some with acute symptoms and others without any symptoms, all were normal.<sup>71a</sup>

*Clinical Features.*—A calcium deposit may be present in one of the tendons of the short rotator cuff without any symptoms, or it may give rise to chronic or acute

84. (a) Dick, G. F.; Hunt, L. W., and Ferry, J. L.: Calcification of the Supraspinatus Tendon: New Treatment, *J. A. M. A.* **116**:1202 (March 22) 1941. (b) Bishop.<sup>69</sup>

85. Bosworth.<sup>71a</sup> Wilson.<sup>39b</sup>

86. Bishop.<sup>69</sup> Bosworth.<sup>71a</sup> Carnett.<sup>71c</sup> Codman.<sup>1b</sup> Emslie.<sup>71d</sup> Thompson and McLaughlin.<sup>49b</sup>

87. Bishop.<sup>69</sup> Bosworth.<sup>71a</sup> Carnett.<sup>71c</sup> Codman.<sup>1b</sup> Dick, Hunt and Ferry.<sup>84a</sup> Emslie.<sup>71d</sup> Wilson.<sup>39b</sup>

88. Bosworth.<sup>71a</sup> Codman.<sup>1b</sup>

89. Bishop.<sup>69</sup> Brickner.<sup>71b</sup> Carnett.<sup>71c</sup> Codman.<sup>1b</sup> Dick, Hunt and Ferry.<sup>84a</sup>

90. (a) Patterson, R. L., Jr., and Darrach, W.: Treatment of Acute Bursitis by Needle Irrigation, *J. Bone & Joint Surg.* **19**:993, 1937. (b) Bishop.<sup>69</sup> (c) Bosworth.<sup>71a</sup> (d) Codman.<sup>1b</sup>

91. Carnett.<sup>71c</sup> Dick, Hunt and Ferry.<sup>84a</sup> Emslie.<sup>71d</sup> Wilson.<sup>39a</sup>

92. Dickson, J. A., and Crosby, E. H.: Periarthritis of the Shoulder: Analysis of Two Hundred Cases, *J. A. M. A.* **99**:2252 (Dec. 31) 1932.

93. Bishop.<sup>69</sup> Bosworth.<sup>71a</sup> Codman.<sup>1b</sup> Patterson and Darrach.<sup>90a</sup> Wilson.<sup>39b</sup>

94. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925, pp. 489-496.

symptoms. The latter may occur suddenly or be superimposed on the former.<sup>95</sup> Calcium deposition in a tendon, noticeable in a roentgenogram may develop rapidly, within two months.<sup>71a</sup> The deposit may immediately give rise to symptoms or may slowly increase in size for years (seven years in one case) with perhaps only slight symptoms.<sup>71a</sup> Schujenioff<sup>96</sup> has found calcium deposition in muscles thirty-six hours after suture. Small deposits may occur and disappear without ever causing symptoms, but a very large one (1.5 cm. in profile) will give rise to symptoms before disappearing.<sup>71a</sup> By means of roentgenograms calcium deposits have been observed to disappear with and without treatment.<sup>85</sup> The deposits are temporary and leave no residual roentgen changes. Perhaps some of the tendon defects seen at autopsy result from absorbed calcium deposits.<sup>1h</sup> An acutely inflamed deposit may rupture into the subacromial bursa, setting up a bursitis.<sup>39b</sup> This may perhaps explain the acute attacks in which there is rapid recovery without treatment.<sup>1h</sup>

**Acute Phase:** An acute attack may appear without warning, often during sleep<sup>97</sup> or during the course of a subacute or chronic attack.<sup>98</sup> There is excruciating pain on any movement of the arm. This pain is felt over the bursa and over the insertion of the deltoid muscle. The deltoid muscle exhibits reflex spasm,<sup>99</sup> which causes limitation of movement. Voluntary fixation eventually leads to actual contracture with limitation of movement from this cause.<sup>99</sup> There is tenderness over the deposit which can be definitely marked out,<sup>100</sup> and in very acute attacks there may be tenderness over the insertion of the deltoid.<sup>101</sup> Atrophy of the spinatus muscles occurs if the symptoms last more than a few weeks.<sup>102</sup> In the acute stage there may be slight fever<sup>103</sup> and leukocytosis.<sup>104</sup> A lump may be felt just medial to the greater tuberosity if the deposit occurs in the supraspinatus tendon.<sup>1h</sup> If untreated, the acute phase may last for several weeks and then revert to a chronic type, may form adhesions or may clear up rapidly if the deposit ruptures into the subacromial bursa.<sup>1h</sup>

**Chronic Phase:** The onset is insidious. First there is an uncomfortable feeling around the shoulder; later it is hard to find a comfortable position in which to rest the arm at night during elevation of the arm in the coronal plane.<sup>105</sup> Pain is most often felt at the fibers of insertion of the deltoid muscle,<sup>106</sup> while the maximum point of tenderness is over the deposit in the tendon<sup>107</sup>; this is most often close to the greater tuberosity, since most of the deposits occur in the supraspinatus tendon. If there has been a long painful period the whole area becomes sensitive,

95. (a) Bosworth, B. M.: Examination of the Shoulder for Calcium Deposits: Technique of Fluoroscopy and Spot Film Roentgenography, *J. Bone & Joint Surg.* **23:567**, 1941. (b) Bishop.<sup>69</sup> Bosworth.<sup>71a</sup> Carnett.<sup>71c</sup> Codman.<sup>1h</sup> Dick, Hunt and Ferry.<sup>81a</sup> Emslie.<sup>71d</sup> Painter.<sup>70</sup> Wilson.<sup>39b</sup>

96. Schujenioff, cited by Harbin<sup>98a</sup> and Moschowitz.<sup>81a</sup>

97. Bosworth.<sup>71a</sup> Codman.<sup>1h</sup> Wilson.<sup>39b</sup>

98. (a) Harbin, M.: Deposition of Calcium Salts in the Tendon of the Supraspinatus Muscle, *Arch. Surg.* **18:1491** (April) 1929. (b) Bishop.<sup>69</sup> (c) Bosworth.<sup>71a</sup> (d) Carnett.<sup>71c</sup> (e) Codman.<sup>1h</sup> (f) Emslie.<sup>71d</sup> (g) Wilson.<sup>39b</sup>

99. Bishop.<sup>69</sup> Codman.<sup>1h</sup>

100. Carnett.<sup>71c</sup> Codman.<sup>1h</sup> Emslie.<sup>71d</sup> Painter.<sup>70</sup> Thompson and McLaughlin.<sup>49b</sup>

101. Carnett.<sup>71c</sup> Codman.<sup>1h</sup> Emslie.<sup>71d</sup>

102. Codman.<sup>1h</sup> Dick, Hunt and Ferry.<sup>81a</sup>

103. Dick, Hunt and Ferry.<sup>81a</sup> Patterson and Darrach.<sup>90a</sup> Thompson and McLaughlin.<sup>49b</sup> Wilson.<sup>39b</sup>

104. Dick, Hunt and Ferry.<sup>81a</sup> Patterson and Darrach.<sup>90a</sup> Wilson.<sup>39b</sup>

105. Bishop.<sup>69</sup> Bosworth.<sup>71a</sup> Carnett.<sup>71c</sup> Codman.<sup>1h</sup> Dick, Hunt and Ferry.<sup>81a</sup> Emslie.<sup>71d</sup> Harbin.<sup>98a</sup> Painter.<sup>70</sup> Wilson (footnotes 4a and 39b).

106. Carnett.<sup>71c</sup> Codman.<sup>1h</sup> Emslie.<sup>71d</sup> Patterson and Darrach.<sup>90a</sup>

107. Carnett.<sup>71c</sup> Codman.<sup>1h</sup> Emslie.<sup>71d</sup> Thompson and McLaughlin.<sup>49b</sup>

with pains shooting up into the neck and down to the hand.<sup>111</sup> This has given rise to the misnomer "brachial neuritis." In some cases the hand may swell and the skin becomes atrophic.<sup>112</sup> There may be a certain amount of spasm and limitation of abduction and external rotation at this point.<sup>113</sup> Acute exacerbations may occur at any time during the chronic course.

*Roentgen Examination.*—Fluoroscopy should be employed and spot roentgenograms taken.<sup>114</sup> The deposit must be seen in profile, or it will be obscured by the underlying bone.<sup>115</sup> Pieces of lead inserted in the tendon were shown to be superimposed on the underlying bone in many positions of the arm, demonstrating the need for fluoroscopic examination.<sup>116</sup> Deposits may be single or multiple<sup>117</sup> and, if liquid, may be seen to change their shape with movement.<sup>118</sup> Sometimes at operation a milky fluid containing calcium is found in the bursa which did not show up on roentgen examination.<sup>119</sup>

*Treatment.*—Acute Stage: The best treatment of the acute attack is prompt excision of the deposit.<sup>120</sup> In experienced hands it is a relatively minor procedure which gives immediate, certain and complete relief. Local or general anesthesia may be used.<sup>121</sup> The average stay in the hospital is four days,<sup>122</sup> and the patient can return to work with unrestricted motion of the shoulder in three weeks.<sup>123</sup> The same incision is used as has been described for exposure of a ruptured supraspinatus tendon. Heat is a valuable adjunct and should be applied locally after operation to speed recovery.<sup>124</sup> Postoperatively only a sling is used.<sup>125</sup>

Irrigation by the two needle method of Patterson and Darrach<sup>126a</sup> has been advocated for acute attacks.<sup>127</sup> It is an operative procedure, and, while good results have been reported by those who favor the method, it is not very satisfactory for solid calcium. The results are not positive, and the deposit, especially if it is a multiloculated one, may easily be missed.<sup>128</sup>

Chronic Stage: The efficacy of treatment of chronic forms is difficult to evaluate, because the patient will get better whatever line of treatment is followed,<sup>129</sup> and even with maltreatment the symptoms will eventually disappear within, at the most, two years.<sup>130</sup> Removal of the calcium by operation gives the most satisfactory result, although recovery is slower than in the case of an acute deposit.<sup>131</sup> The use of an overhead pulley aids in regaining abduction. If the choice is left to the patients, the majority will elect some form of heat therapy, and over a period of time they will recover.<sup>132</sup> Under treatment with diathermy<sup>133</sup> the deposits disappear in two and one-half to eleven weeks,<sup>134a</sup> but the patient endures intense pain for a week

108. Carnett.<sup>11c</sup> Codman.<sup>1h</sup> Painter.<sup>70</sup>

109. Bishop.<sup>69</sup> Codman.<sup>1h</sup>

110. Bishop.<sup>69</sup> Codman.<sup>1h</sup> Emslie.<sup>71d</sup> Painter.<sup>70</sup>

111. Bishop.<sup>69</sup> Bosworth (footnotes 71 a and 95 a).

112. Bishop.<sup>69</sup> Bosworth (footnotes 71 a and 95 a). Codman.<sup>1h</sup> Dick, Hunt and Ferry.<sup>84a</sup> Emslie.<sup>71d</sup>

113. (a) Hitzrot, J. M.: Surgical Diseases of the Shoulder Bursae, Ann. Surg. 98:273, 1933. (b) Bosworth.<sup>71a</sup> Codman.<sup>1h</sup> Moseley.<sup>18a</sup>

114. Bosworth.<sup>71a</sup> Brickner.<sup>71b</sup> Codman.<sup>1h</sup> Emslie.<sup>71d</sup> Painter.<sup>70</sup> Rogers.<sup>71f</sup> Thompson and McLaughlin.<sup>49b</sup> Wilson.<sup>39b</sup>

115. Bosworth.<sup>71a</sup> Moseley.<sup>18a</sup> Painter.<sup>70</sup>

116. Carnett.<sup>71c</sup> Codman.<sup>1h</sup>

117. Bishop.<sup>69</sup> Patterson and Darrach.<sup>126a</sup> Wilson.<sup>39b</sup>

118. Bosworth.<sup>71a</sup> Moseley.<sup>18a</sup>

119. Carnett.<sup>71c</sup> Emslie.<sup>71d</sup>

120. (a) Troedsson, B. S.: Diathermy for Calcium Deposits Around Subacromial Bursa and Supraspinatus Tendon, Arch. Phys. Therapy 19:166, 1938. (b) Nilssen, L.: Results of Various Methods of Treatment of Peritendinitis Calcificans of Shoulder Region, Med. rev., Bergen 51:67, 1934; cited by Troedsson.



or so. The increased vascularity and resulting high carbon dioxide content of the tissue caused by diathermy<sup>64b</sup> makes the medium acid, so that calcium is absorbed. The use of immobilization in abduction causes adhesions and is mentioned only to be condemned.<sup>71a</sup>

#### IV. SUBACROMIAL BURSITIS

This subject must be included because the subacromial bursa is so frequently involved by lesions affecting primarily the tendons of the short rotators of the shoulder. Subacromial bursitis never arises as a primary condition. The bursa is a limiting structure which is involved only by lesions in the surrounding structures.<sup>121</sup> Codman<sup>11</sup> and Wilson<sup>39b</sup> believed that the bursa is more sensitive to pain than the surrounding structures. Calcification or rupture of the supraspinatus tendon gives rise to a bursitis.<sup>122</sup> These have been adequately considered in the preceding sections of this review. Tuberculosis of the subacromial bursa has been described but rarely.<sup>123</sup>

It is with trepidation that the last entity is introduced. It is the so-called "periarthrititis" or "tendinitis" or "frozen shoulder." This is a condition in which physical examination fails to reveal any swelling or definite point of local tenderness, although there may be definite sensitiveness about the shoulder. There is limitation of both passive and active abduction. If the shoulder girdle is fixed, abduction will not exceed 35 to 45 degrees. If movement is forced, pain is elicited.<sup>124</sup> When the condition is treated by abduction, as advocated by Sir Robert Jones, loud snapping sounds are heard, followed by complete freeing of the movements of the shoulder.<sup>75</sup> If the bursa is opened the results are disappointing. There may be adhesions in the bursa, but usually there are none. With the finger on the base of the bursa, the snapping of adhesions in the tendinocapsular structure beneath the finger may be felt as the arm is manipulated.<sup>75</sup> Codman<sup>11</sup> and Wilson<sup>39b</sup> both have reported occasionally finding the base of the bursa reddened, and they both felt that this represented the onset of the condition. It may also arise as a sequel of rupture or calcification of the supraspinatus tendon.<sup>39b</sup> The onset of the condition is gradual over the course of several months.

In the treatment of the so-called "frozen shoulder," many authors,<sup>125</sup> using different methods, have reported good results. Given time, two years at the very most, and no treatment at all, the condition will clear up by itself.<sup>11</sup> Time is the element common to all methods of treatment.<sup>18a</sup> However, good treatment will cut down the amount of time required.<sup>11</sup> Mild forms will clear up with massage, heat and exercise.<sup>126</sup> The simplest and most effective treatment for the completely frozen shoulder is the hyperabduction treatment of Codman.<sup>11</sup> The patient is put to bed, the forearm splinted and the splint tied to the head of the bed, which is raised by blocks under the legs if necessary to secure sufficient extension. A small dose of morphine may be given to secure relaxation but not enough to remove pain entirely. In twelve to twenty-four hours the spasm, which contributes to the symptoms, yields, the adhesions give, the greater tuberosity passes under the acromion and the arm becomes abducted and externally rotated. In a day or two the splint is removed and a bandage is tied loosely around the wrist to the head of the bed. The patient gets up daily and carries out exercises bending forward from the hips and letting

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121. Codman.<sup>11</sup> Moseley.<sup>18a</sup> Rogers.<sup>71f</sup> Wilson.<sup>39b</sup>  
 122. Brickner.<sup>71b</sup> Codman.<sup>11</sup> Ferguson.<sup>37</sup> Moseley.<sup>18a</sup> Rogers.<sup>71f</sup> Wilson.<sup>39b</sup>  
 123. Brickner.<sup>71b</sup> Hitzrot.<sup>113a</sup>  
 124. Codman.<sup>11</sup> Ferguson.<sup>37</sup> Rogers.<sup>71f</sup> Wilson.<sup>39b</sup>  
 125. Codman.<sup>11</sup> Ferguson.<sup>37</sup> Moseley.<sup>18a</sup> Rogers.<sup>71f</sup> Wilson.<sup>39b</sup>  
 126. Codman.<sup>11</sup> Rogers.<sup>71f</sup> Wilson.<sup>39b</sup>

the arms hang down. The patient stays in the hospital until he can move the arm about in any direction over the head, usually one or two weeks. For a few weeks after discharge he takes stooping exercises and sleeps with his arm in an abducted position. Wilson<sup>25b</sup> also uses a modified form of the hyperabduction method. Heat (diathermy, electric pad or fomentations) may be of some help.<sup>127</sup> Should the patient not wish to go to bed the manipulation method of Moseley<sup>12a</sup> will give good results for the completely frozen shoulder in a little longer time than the recumbent hyperabduction method. In the case of a shoulder involved to a lesser degree it is probably the method of choice. The area of the subacromial bursa is infiltrated with 50 cc. of 1 per cent solution of procaine hydrochloride, and the shoulder is then manipulated, if possible, through its complete range of movement. Manipulation is followed by twenty minutes of diathermy treatment. The treatment is repeated at intervals until the normal range of painless movement is regained.

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127. Codman.<sup>1b</sup> Moseley.<sup>12a</sup> Rogers.<sup>71c</sup>

# EFFECTS OF ADMINISTRATION OF SODIUM SULFADIAZINE TO DOGS

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Changes attributed to sulfonamide compounds have been reported by other investigators.<sup>1</sup> We<sup>2</sup> recently reported lesions in dogs produced by sodium sulfadiazine (the monohydrate sodium salt of 2-[paraaminobenzenesulfonamido]-pyrimidine), and similar lesions in the kidney of man have been recorded.<sup>3</sup>

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- Since this paper was submitted for publication an additional case of nephrosis due to sulfonamide compounds has been reported (Sulfonamide Nephrosis, Cabot Case 28501, *New England J. Med.* **227**:922-927, 1942). Renal phlebitis and multinucleated giant cell changes were striking in this case.

To study the effects of sulfadiazine and of the combination of sulfadiazine and ether anesthesia on the liver, kidney and reticuloendothelial system, the following procedures were employed.

#### METHOD

Ten mongrel dogs each weighing from 6.2 to 16.4 Kg. were used in the first experiment. Blood was withdrawn for erythrocyte and leukocyte counts, and differential leukocyte and platelet counts were made on blood smears. Determinations of hemoglobin, hematocrit reading, icterus index and prothrombin were made. The urine was examined microscopically; the heat-acid test for the presence of proteins was done, and the acidity or alkalinity was determined with litmus paper.

With the animal under anesthesia induced with sodium pentobarbital, administered intravenously, the abdomen was opened aseptically. Four or five grams of liver was excised, and the abdomen was closed. The glycogen and total carbohydrates in the liver were determined chemically, and sections were stained with Best's carmine stain for glycogen, in addition to routine hematoxylin and eosin stains.

At intervals during the ensuing two weeks, blood was withdrawn for the determinations mentioned previously.

Beginning two weeks after operation, 0.1 Gm. of sodium sulfadiazine per kilogram of body weight was administered twice daily to 6 animals for two weeks. The drug was injected subcutaneously in a 20 per cent aqueous solution. During the two week period blood was frequently withdrawn for the determinations listed, and in addition the levels of the drug in the blood and in the urine were determined. The urine was examined for the presence of protein, blood elements and crystals and for the reaction to litmus paper.

Four weeks after the first operation, under drop ether anesthesia, the 6 treated animals and the 4 controls were again subjected to laparotomy, and a second biopsy specimen was obtained from the liver. The animals were maintained in the surgical plane of anesthesia for three hours, and at the end of this time the studies of the blood and urine were repeated and the animals were killed by injection of ether into the heart. The biopsy specimens from the liver were studied in the manner previously indicated.

At autopsy all organs except the brain, spinal cord, gallbladder, thyroid and parathyroids were examined. Specimens of heart, lung, liver, pancreas, spleen, kidney, urinary bladder, adrenal, thoracic aorta, inferior vena cava, stomach, small intestine, appendix, sternal and costal marrow, skeletal muscle and tissues from the area into which the solution of sodium sulfadiazine had been injected were taken for microscopic examination.

The microscopic observations to be described suggested a study to determine whether the pathologic changes were due to a combination of sodium sulfadiazine, sodium pentobarbital and ether or to sodium sulfadiazine alone.

To a second group of 8 dogs sodium sulfadiazine was administered as it had been to the first group, and treatment was continued up to the time the animal died or was killed. One of the treated animals was killed after eight days and 1 after twenty-one days. Deaths of the remainder occurred at six, nine, ten, twelve, thirteen and eighteen days. The animals which died at six and at ten days had minimal bronchopneumonia that might have been a factor contributory to the cause of death; the deaths of the others were apparently due to sodium sulfadiazine.

The studies in this second group were limited to the determination of the concentration of sulfadiazine in the blood, the urea nitrogen content of the blood and the arterial pressure as measured by femoral puncture. Postmortem examination was done on all animals. In addition to the 4 controls noted previously, 4 apparently normal dogs were killed and used as controls for histologic examination.

#### RESULTS

1. There were no significant changes in the values for prothrombin, glycogen or total carbohydrate or in the icterus index.

2. A normocytic hyperchromic anemia developed in the 6 treated animals in which the blood picture was studied. No significant changes were noted in the leukocyte, differential cell or platelet counts.

3. The urine of all animals was acid to litmus paper and consistently showed proteinuria and the presence of blood elements, casts and sulfadiazine crystals. In the urine of 6 animals studied on the fourteenth day of treatment, the concentrations of sulfadiazine ranged from 203 to 240 mg. per hundred cubic centimeters.

4. The maximum concentrations of sulfadiazine in the blood were in general high (fig. 1). Ten dogs had maximum levels between 40 and 120 mg. per hundred cubic centimeters. Two dogs had maximum levels of 25, 1 a maximum of 20 and 1 a maximum of 17 mg. per hundred cubic centimeters.

5. In the 8 animals of the second group, there was a marked elevation of the urea nitrogen content of the blood, (fig. 2) the maximum being 111 mg. per

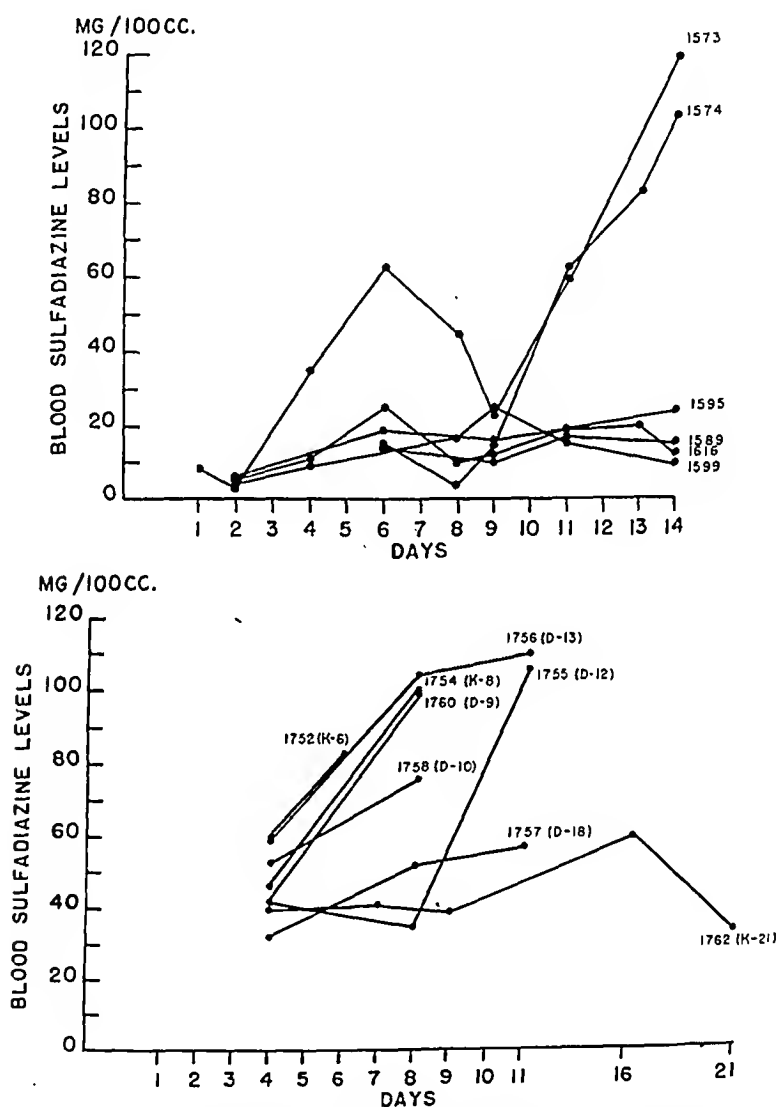


Fig. 1.—Upper chart, concentrations of sulfadiazine in the blood of a group of experimental animals. Lower chart, concentrations of sulfadiazine in the blood of a group of experimental animals. The time of death (D) or killing (K) is recorded.

hundred cubic centimeters. This elevation tended to follow the level of blood concentration of sulfadiazine (fig. 3).

6. There was a moderate elevation of arterial blood pressure (140 to 160) in 3 animals, a slight elevation (130 to 140) in 2 animals and no elevation (80 to 110) in 2 animals.

7. Grossly, there was sloughing at the sites of injection of the drug in about half the animals. A minimal lobular pneumonia, as previously mentioned, was

found in 2 of the dogs of the second group. There were no gross pathologic changes other than the presence of fine yellow refractile streaking in the pyramids of the kidney, crystals in the renal pelvis and calices, and slight swelling of the renal parenchyma of all animals. Chemical analysis of the crystals showed that from 70 to 75 per cent of the material was free sulfadiazine and that the remainder was the combined or acetylated form.

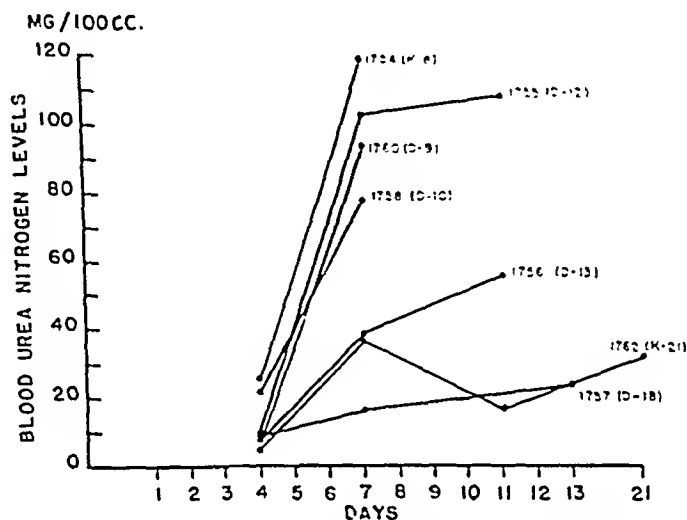


Fig. 2.—Levels of urea nitrogen in the blood. The time of death (D) or killing (K) is recorded.

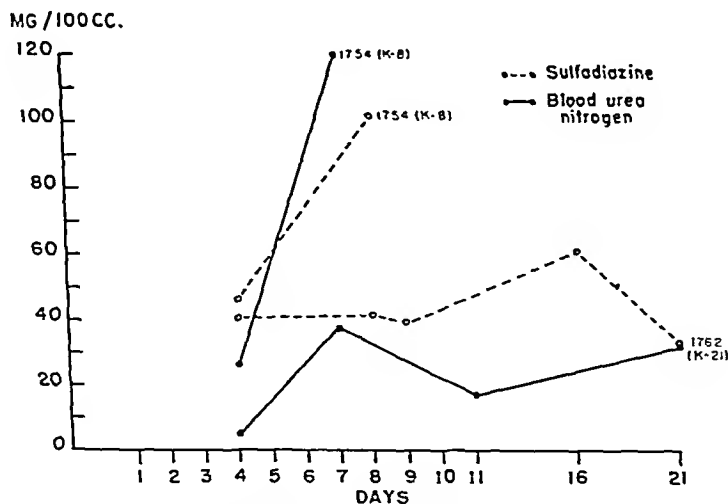


Fig. 3.—There is a rough correlation between a rising level of urea nitrogen in the blood and an elevated level of sulfadiazine.

8. Microscopic pathologic changes were found in the kidneys, spleen, liver, heart and bone marrow and in the tissues removed from the site of injection of the sodium sulfadiazine. These changes were not present in 8 control dogs.

The changes in the kidneys of all animals were most striking. The nephron, the vascular bed and the stroma were simultaneously affected as early as the sixth

day. The characteristics of these changes became more obvious in the animals which received the sodium sulfadiazine for longer periods.

The changes in the glomeruli were first indicated by the escape of blood and protein into Bowman's clear space. Later inflammation developed about the glomeruli, characterized by the presence of monocytes, lymphocytes, plasma cells and a very small number of polymorphonuclear eosinophils and neutrophils. Finally fibroblasts developed and collagen was laid down, forming a granuloma (figs. 4 and 5).



Fig. 4.—Glomerular granuloma showing inflammatory reaction ( $\times 300$ ).

The tubular system of all animals was simultaneously affected, particularly the proximal and distal convoluted tubules and the collecting tubules. The lining cells were swollen, and the cell outlines were not distinct. The nuclei were frequently pyknotic and were often absent. The tubules frequently contained casts of desquamated lining cells. Many of the tubular lining cells were in mitosis. An inflammation similar to that about the glomeruli developed in the stroma about the affected tubules.

The kidney tubules were often filled with a hyaline protein material, metachromatic in its staining qualities. The casts were most often glassy blue and infrequently pink or yellow-brown. In many areas the protein material had escaped into the interstitial tissues through an area of necrosis of the tubular lining cells.

and the basement membrane. Inflammation in which monocytes, epithelioid cells, lymphocytes and plasma cells were prominent occurred in these areas. Later fibroblasts grew in and collagen was laid down, and after twenty-one days multinucleated giant cells developed forming a giant cell granuloma (fig. 6).

Crystals of sulfadiazine were found in the cortical and pyramidal tubules of 12 dogs. The crystals were present, many times in a protein cast, as high in the nephron as the descending loop of Henle. The sulfadiazine crystals were found in the calices and pelves of all animals. An inflammatory reaction consisting of cell elements similar to those which developed in the cortical and pyramidal stroma occurred in the submucosal tissues of the calices and pelves of 13 animals (fig. 7).



Fig. 5.—Glomerular granuloma showing fibrosis ( $\times 285$ ).

In the walls of and about several of the renal veins of 9 animals, an inflammatory reaction developed which was largely mononuclear in type, with occasional polymorphonuclear eosinophils and neutrophils. Often a mural thrombus was attached to the walls of veins at sites of inflammation. Several small veins were completely thrombosed, and about them fresh hemorrhage was present in the interstitial tissues. A similar sort of inflammation affected the hepatic veins of 3 animals, but no thrombi were noted.

About several of the arteries of the kidneys and occasionally about the arteries of the heart and the liver there was a perivascular leukocyte reaction consisting predominantly of mononuclear leukocytes. Occasionally a few polymorphonuclear eosinophils and neutrophils were present (fig. 8).



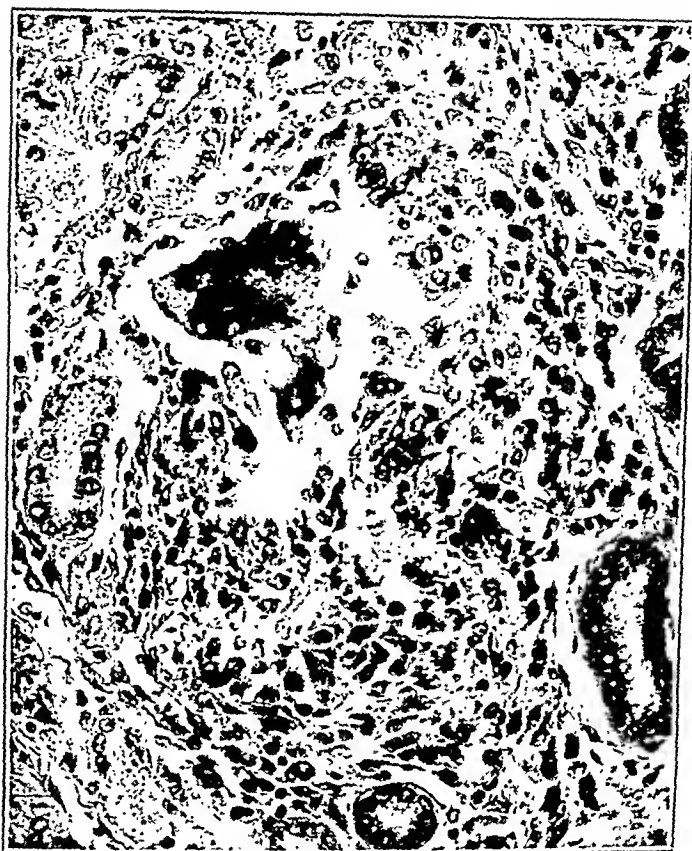


Fig. 6.—Interstitial giant cell granuloma of the renal cortex ( $\times 290$ ).

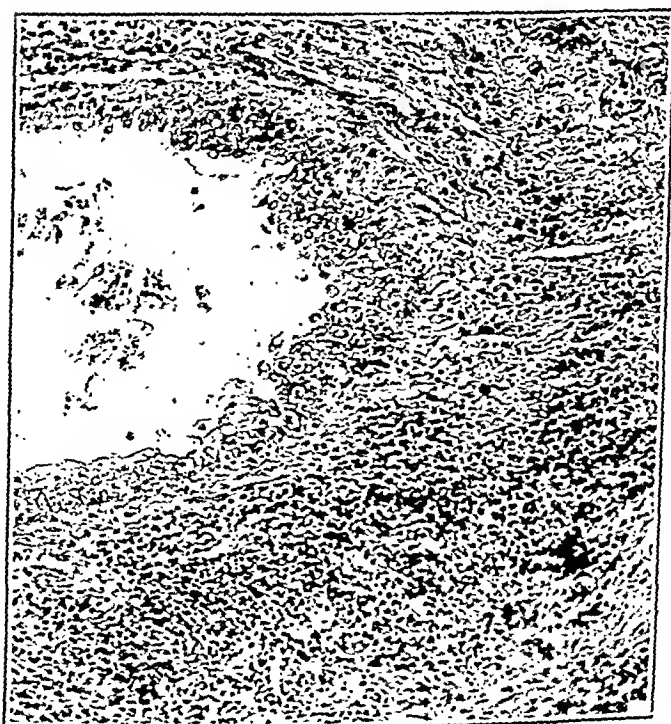


Fig. 7.—Inflammation in the submucosa of the calix ( $\times 150$ ).

The parenchyma of the liver was normal in appearance in all animals. In 12 animals the Kupffer cells were filled with hemosiderin.

In the spleen all animals had large amounts of both intracellular and extracellular hemosiderin. There was a striking change of the germinal centers characterized by the presence of cellular debris and mononuclear phagocytes, commonly referred to as "toxic" change.

The sternal marrow of 8 animals showed a moderate hyperplasia of all elements, particularly of the erythrogenic series. The marrow of 4 animals contained small areas of recent hemorrhage. In the marrow of 7 dogs there was a moderate amount



Fig. 8.—Renal artery showing perivascular leukocytic infiltration ( $\times 580$ ).

of hemosiderin in large mononuclear phagocytes. Five animals had either no change or a slight hypoplasia of the marrow. There was a rather marked hypoplasia of the sternal marrow of a single dog. There were small areas of necrosis of the marrow of another animal, and in these areas large mononuclear phagocytes were filled with eosinophilic debris.

Occasional granulomas, consisting of lymphocytes, plasma cells, monocytes, fibroblasts and collagen, were found in the myocardium in 2 animals. The myocardium of 1 dog was the site of small areas of recent hemorrhage.

The tissues taken from the sites of injection of the aqueous solution of sodium sulfadiazine showed almost no loss of tissue-staining quality. Crystals of sulfadiazine were included in multinucleated foreign body giant cells, and there was a

small amount of organizing hemorrhage in these areas. The almost complete absence of polymorphonuclear neutrophil leukocytes from the inflammatory reaction in these areas was striking. The inflammatory reaction was predominantly mononuclear in type, consisting of many monocytes and a moderate number of lymphocytes and plasma cells.

#### COMMENT

These studies indicate that sodium sulfadiazine injected subcutaneously into dogs produces pathologic changes of the bone marrow, blood, blood vessels and kidneys. The combination of ether anesthesia and sulfadiazine did not alter the changes found following the use of the drug alone.

That renal physiology is disturbed is suggested by the retention of nitrogenous waste products and the elevation of blood pressure in some animals and the development of proteinuria and hematuria in all animals. Hematuria often occurred prior to the development of sulfadiazine crystals in the urine and indicated a primary injury to the renal structures, independent of the effect of tubular obstruction produced by the precipitation of sulfadiazine crystals in the nephron. That sulfadiazine is retained by damaged kidneys is suggested by the high blood levels that developed late in the period of administration.

Sulfadiazine crystals were precipitated not only in the pelvis and collecting tubules but as high in the nephron as the descending loop of Henle. Many subcapsular tubules contained the crystals. Acidity of the urine may be an important factor affecting the precipitation of this drug, and further studies are desirable to ascertain whether the renal damage can be controlled by alkalization of the urine.

The inflammatory reaction and the granulomas which occurred in the stroma about degenerating tubules and about the pelvis and calices is probably due to irritation by the drug or its product that has escaped into the stroma. These inflammations are characterized by the predominance of mononuclear leukocytes. It is noteworthy that a similar inflammation occurred in the tissues at the site of injection of the aqueous solution of the sodium sulfadiazine. This suggests that both are due to the sulfadiazine or to some changed form of the drug.

The damage to glomeruli and tubules may terminate in the destruction of these structures with formation of a granulomatous lesion, and recovery of a nephron thus scarred seems unlikely. However, most nephrons are not scarred.

Deaths of at least 4 dogs, and probably of 6, of the second group must be attributed to sodium sulfadiazine and were evidently the consequence of damage to the kidneys and the resultant uremia.

The mechanism of the development of hyperchromic anemia is obscure. That erythrocytes are destroyed is indicated by the presence of hemosiderosis in the bone marrow, the spleen and the liver. The hyperplasia of the bone marrow in some animals is probably a response to the destruction of erythrocytes.

#### SUMMARY AND CONCLUSIONS

Dogs given subcutaneous injections of a 20 per cent aqueous solution of sodium sulfadiazine had initial blood levels of 10 to 15 mg. per hundred cubic centimeters. Within a few days renal insufficiency with rising levels of urea and sulfadiazine in the blood set in, and several of the dogs died in one to three weeks. Some showed a rise in arterial blood pressure; all showed proteinuria and hematuria.

In addition to the deposits of sulfadiazine precipitated in the renal tubules and renal pelvis with granulomatous reactions about them, there were perivascular and even some glomerular granulomas. Instances of phlebitis and interstitial reaction in the kidney and other viscera were more numerous than those reported in other

investigations of the toxicity of sulfonamide compounds. Focal necrosis in bone marrow occurred in 1 of 14 dogs, and hypoplasia of the bone marrow occurred in another. All animals had evidence of hemolytic anemia. Degenerating germinal centers were present in the spleen in nearly all.

Although there was no change in platelets or prothrombin, some visceral petechial hemorrhages were noted. There was no apparent damage to the liver.

The dog, which has an acid urine, shows unusually severe renal damage from doses of sulfadiazine within the therapeutic range. Extrarenal perivascular inflammation is also striking. The relative importance of parenteral deposits of the drug and of the acidity of the urine as factors predisposing to these severe lesions has not been determined.

Women are affected more frequently than men. Grouping the statistics of the four largest groups of cases reported,<sup>2</sup> we find the ratio to be 142 women to 107 men. Of the patients in the group on which we are reporting, 4 were women and 6 were men.

The incidence is greatest among those from 50 to 60 years of age. The average age in this series was 55.9 years, with the youngest patient 31 and the oldest 73 years of age. Keyes<sup>2a</sup> reported 57 years as the average age; Raiford,<sup>1c</sup> 48.9 years. All investigators have noted a wide variation in age.

Sufficient data have accumulated to establish antecedent lesions as important causative agents of anal carcinoma. Drueck<sup>1d</sup> went so far as to say that such a tumor always arises on the basis of some previous condition characterized by chronic irritation. Buie and Brust<sup>1b</sup> noted a history of an antecedent lesion in 34 of their 51 cases. As stressed by Rosser<sup>3</sup> and observed by many others,<sup>4</sup> chronic fistulas and scars resulting from fistulectomy are the lesions which have given rise to carcinoma most often. Carcinoma may also arise on the basis of leukoplakia,<sup>3c</sup> a fissure,<sup>3a</sup> hemorrhoids,<sup>2a</sup> venereal condyloma<sup>1f</sup> or an irradiation scar.<sup>2a</sup>

The clinical significance of these causative factors warrants consideration. From a diagnostic viewpoint, carcinoma should be kept in mind in dealing with all rectal and anal lesions, no matter how obviously benign they may appear. A biopsy should be made whenever there is the slightest suspicion of malignancy. Chronicity alone is an ample indication for the microscopic examination of a lesion. All tissue removed during the operative treatment of a supposedly benign lesion should be sent for pathologic diagnosis. This practice is followed at the Mayo Clinic, where it has led to the detection of carcinoma in at least 1 case after microscopic examination of supposed hemorrhoidal tissue.<sup>1b</sup> The pressure of malignant growth was not suspected when the hemorrhoidectomy was performed.

After treatment, operative or conservative, of a benign lesion, it is wise to have the patient report his condition at intervals. If this is not feasible, he should be instructed to seek medical attention promptly if symptoms appear again, for the later episode may possibly be the first evidence of a carcinoma rather than a mere recurrence of the original condition.

Several epidermoid carcinomas arising in irradiated anal skin have been reported.<sup>2a</sup> It is worthy of note that carcinoma has not been reported arising on a basis of uncomplicated pruritus.<sup>3c</sup>

Wassermann tests of the blood gave positive results in 3 cases of anal epithelioma reported by Hankins.<sup>1f</sup> He and several others<sup>3b</sup> have expressed the opinion that syphilis plays a causative role. Whether or not this is true, one should remember that anal cancer may masquerade as syphilis. Wassermann tests of the blood gave negative results in 8 of our cases and were not made in the remaining 2 cases.

One of the 10 patients whose cases we are presenting had a history of a recurrent fistula dating back twenty years. An antecedent lesion was not mentioned by the other 9 patients.

2. (a) Keyes, E. L.: Squamous Cell Carcinoma of the Lower Rectum and Anus. *Ann. Surg.* **106**:1046-1058 (Dec.) 1937. (b) Bensaude, R.; Cain, A.; Oury, P., and Poirier, A.: Le cancer de l'anús, *Presse méd.* **41**:1837-1842 (Nov. 18) 1933. (c) Kerr, J. G.: Squamous Cell Carcinoma of the Anorectal Region, *Texas State J. Med.* **36**:548-551 (Dec.) 1940. (d) Raiford.<sup>1c</sup>

3. Rosser, C.: (a) Cancer of the Anal Canal, *South. M. J.* **28**:527-528 (June) 1935; (b) Fistula: An Etiologic Factor in Cancer of the Anal Canal, *Texas State J. Med.* **30**:203-207 (July) 1934; (c) The Etiology of Anal Cancer, *Am. J. Surg.* **11**:328-333 (Feb.) 1931; (d) Relation of Fistula in Ano to Cancer of Anal Canal, *Tr. Am. Proct. Soc.* **35**:65-71, 1934.

4. Raiford.<sup>1c</sup> Hankins and Harding.<sup>1f</sup> Keyes.<sup>2a</sup>

There is no symptom complex characteristic of anal carcinoma. Rectal pain, occurring chiefly at stool, is the most frequent presenting symptom. Small, repeated rectal hemorrhages are commonly observed. These may take the form of a persistent bloody, mucoid anal discharge. Diarrhea or constipation may be noted, the former more frequently. However, by diarrhea the patient most likely means the frequent passage of small stools or an anal discharge such as has already been described rather than true diarrhea. Itching and irritation around the anus often occur. Less commonly, an anal tumor is the presenting complaint, while in several of the cases reported in the literature<sup>5</sup> enlarged inguinal nodes first attracted the patient's attention.

Six of the patients in our series complained of rectal bleeding, 5 of rectal pain, 4 of diarrhea, 3 of loss of weight, 2 of hemorrhoids, 2 of constipation, 1 of rectal prolapse, 1 of fistula and 1 of anal discharge. These symptoms may occur singly or in any combination. It is obvious that they are no more typical of carcinoma than they are of a number of other rectal diseases.

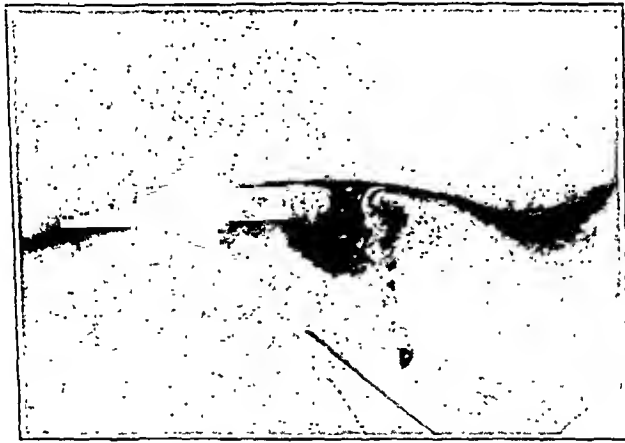


Fig. 1.—An additional tumor seen in 1941. Epidermoid carcinoma of the anus extending into the right ischiorectal fossa and presenting as an ulcerating cutaneous lesion.

Buie and Brust<sup>1b</sup> reported the average duration of symptoms prior to the time of seeking medical attention as eleven months; Keyes,<sup>2a</sup> as eighteen months. In the 9 cases of this series in which figures were available, the average duration of symptoms was twelve months. However, in 7 of these 9 cases the duration was three months or less.

There is a wide variation in the gross appearance of this type of epidermoid carcinoma (fig. 1). It may simulate a fistula, fissure, chancre, condyloma or hemorrhoid or any other anorectal disease, including, of course, adenocarcinoma. In general the growth tends to be of one of two types: It may be nodular or warty, or it may be flat or craterous. The elevated tumor is often ulcerated; the flat one, nearly always so. Both types are usually of firm consistency, the flat tumor having a hard, granulating base and a firm, rolled edge. It does not seem profitable to enter into further descriptive detail since this aspect of the subject has been so ably dealt with elsewhere. Bensaude and his associates<sup>2b</sup> presented a complete gross description, illustrated by numerous accurate and distinct color reproductions. The papers of Raiford<sup>1c</sup> and Drueck<sup>1d</sup> also contain full descriptions of the gross appearance. Positive diagnosis can be established only by microscopic sections.

5. Keyes,<sup>2a</sup> Bensaude and others,<sup>2b</sup>

Anatomically, the term anus is being used in its broad sense and refers to the perianal and anal skin as well as to the anal canal, which extends upward for a short distance beyond the mucocutaneous junction. Accordingly, anal carcinomas arising from the anal or perianal skin may be located entirely externally, while those arising at the mucocutaneous juncture, a far more common site of origin, tend to extend upward into the anal canal and often into the lower part of the rectum. We feel that the histologic nature of the tumor is more important than its precise location when one is deciding whether or not a growth is anal. A squamous cell tumor in the anal canal or the lower part of the rectum may safely be assumed to have arisen in the anal skin or mucocutaneous junction, though it comes to lie predominately above these sites. In rare instances a primary epidermoid carcinoma may be found in the colon or the upper part of the rectum. The origin of such a tumor is to be explained only on the basis of cellular metaplasia.<sup>6</sup> An instance of a growth in this location is included in the group of 10 cases which we are presenting, not because we believe that the tumor in this case was related to the anus in any way but because we feel that the rarity of the situation warrants reporting the case.

Epidermoid carcinoma of the anus is similar histologically to epidermoid carcinoma of the skin elsewhere on the body. Some of the growths are well differentiated, being characterized by a uniform type of cell and by epithelial pearls (fig. 2). Conversely, others exhibit a cellular arrangement devoid of order, with a marked variation in the size and shape of individual cells; numerous giant cells and cell nuclei in all states of mitosis may be present (fig. 3). Still other tumors may show histologic types lying anywhere between these extremes of differentiation. Also, the degree of differentiation may vary within the same tumor, as was noted in 2 of our 10 cases (cases 4 and 6). This variation in histologic nature may best be expressed in terms of grading. Kerr,<sup>2c</sup> on the basis of Broders' criteria, found that in the 80 cases of squamous cell carcinoma of his series in which reports were available 4 growths were of grade 1, 17 of grade 2, 41 of grade 3 and 18 of grade 4.

The tumors in the 10 cases which we are reporting were studied and graded microscopically in the laboratory of Dr. Shields Warren. Five of the tumors were found to be of grade 1, 1 of grade 2 and 2 of grade 3. The remaining 2 tumors varied within themselves, 1 showing characteristics of grades 1 and 2 and the other of grades 2 and 3. The possible value of grading in relation to treatment will be referred to later.

Too great emphasis cannot be placed on the importance of the manner of spread of epidermoid carcinoma of the anus, both locally and by metastasis, since this is the basis for treatment. Locally, it may invade the sphincter ani muscles, the perianal tissue, the rectovaginal septum or the prostate gland, or it may extend upward into the rectal wall and rectum.

Metastasis may occur by way of lymphatics or blood vessels. That metastases may be blood borne has been established beyond any doubt. Tumorous invasion of blood vessels (fig. 4) was noted microscopically in the sections from 2 of our cases (cases 9 and 10). Further and conclusive evidence is provided through the fact that metastases to the liver have been observed.<sup>7</sup> These could hardly have occurred by any route except that of the portal venous system. However, metastases to the liver were noted only twice in a group of over 200 cases collected from the literature of the last decade. It is thus apparent that blood-borne meta-

6. Manning, V. R.: Adenocarcinoma of the Anus, *Tr. Am. Procl. Soc.* 38:70-74, 1937. Raiford.<sup>1c</sup>

7. Buie and Brust.<sup>1b</sup> Bensaude and others.<sup>2b</sup>

tases are sufficiently uncommon for the possibility of their presence to be disregarded when treatment of the initial lesion is contemplated. In both our cases in which invasion of blood vessels was noted microscopically, abdominoperineal resection was performed, so that abdominal exploration was possible. No evidence of metastatic tumor was noted in the abdomen of either patient. Blood-borne metastases to other organs are rare.

On the other hand, lymphatic metastases are common, and it is the possible or actual presence of these which is most important in the formulation of any

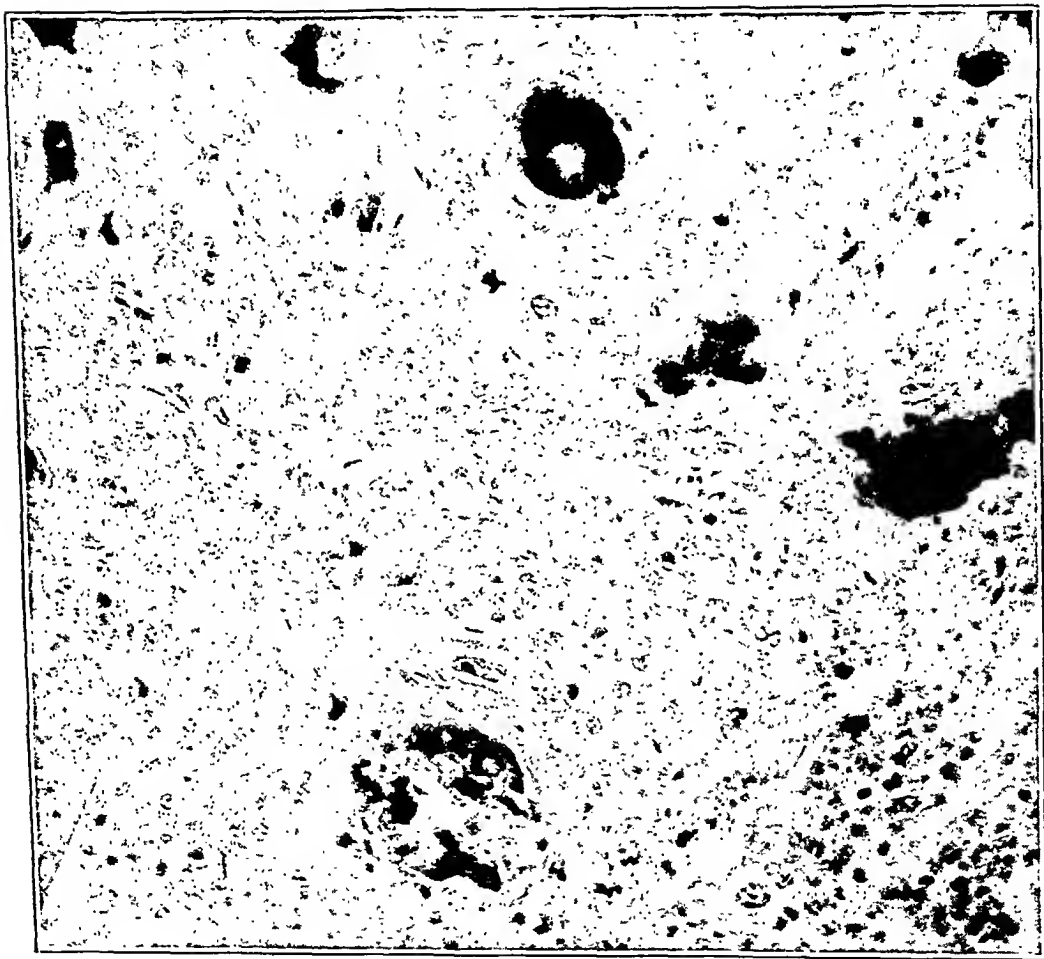


Fig. 2 (case 4).—This tumor is well differentiated. The cells are uniform, but many mitotic figures are noted. Epithelial pearls are present. The tumor was graded 1 and 2 on the basis of this and other sections. The growth had invaded the rectum and metastasized to a node 8 cm. above. The patient died of recurrence in the posterior wound four months after abdominoperineal resection.

plan of treatment. The lymphatic routes of spread of epidermoid carcinoma of the anus are well known and have recently been described in detail by Keyes.<sup>2a</sup> He stressed the fact that metastases from such a tumor are confined almost without exception to the downward and lateral zones of spread described by Miles<sup>8</sup>

8. Miles, W. E.: The Pathology of the Spread of Cancer of the Rectum and Its Bearing upon the Surgery of the Cancerous Rectum. *Surg., Gynec. & Obst.* 52:350-359 (Feb.) 1931.



and to the inguinal lymph nodes. The downward zone of spread of Miles consists of the perianal skin, the sphincter ani muscle and the ischiorectal fat. Keyes found this zone to be the one most often involved by metastasis. The lateral zone of spread refers to the levator ani and coccygeal muscles, the pelvic peritoneum, the prostate gland, the base of the urinary bladder, the cervix uteri and the base of the broad ligament. Keyes noted that this zone was involved almost as frequently as the downward zone. He further noted that in his cases the upward zone of spread of Miles, including the rectorectal nodes, the pelvic mesocolon, the para-

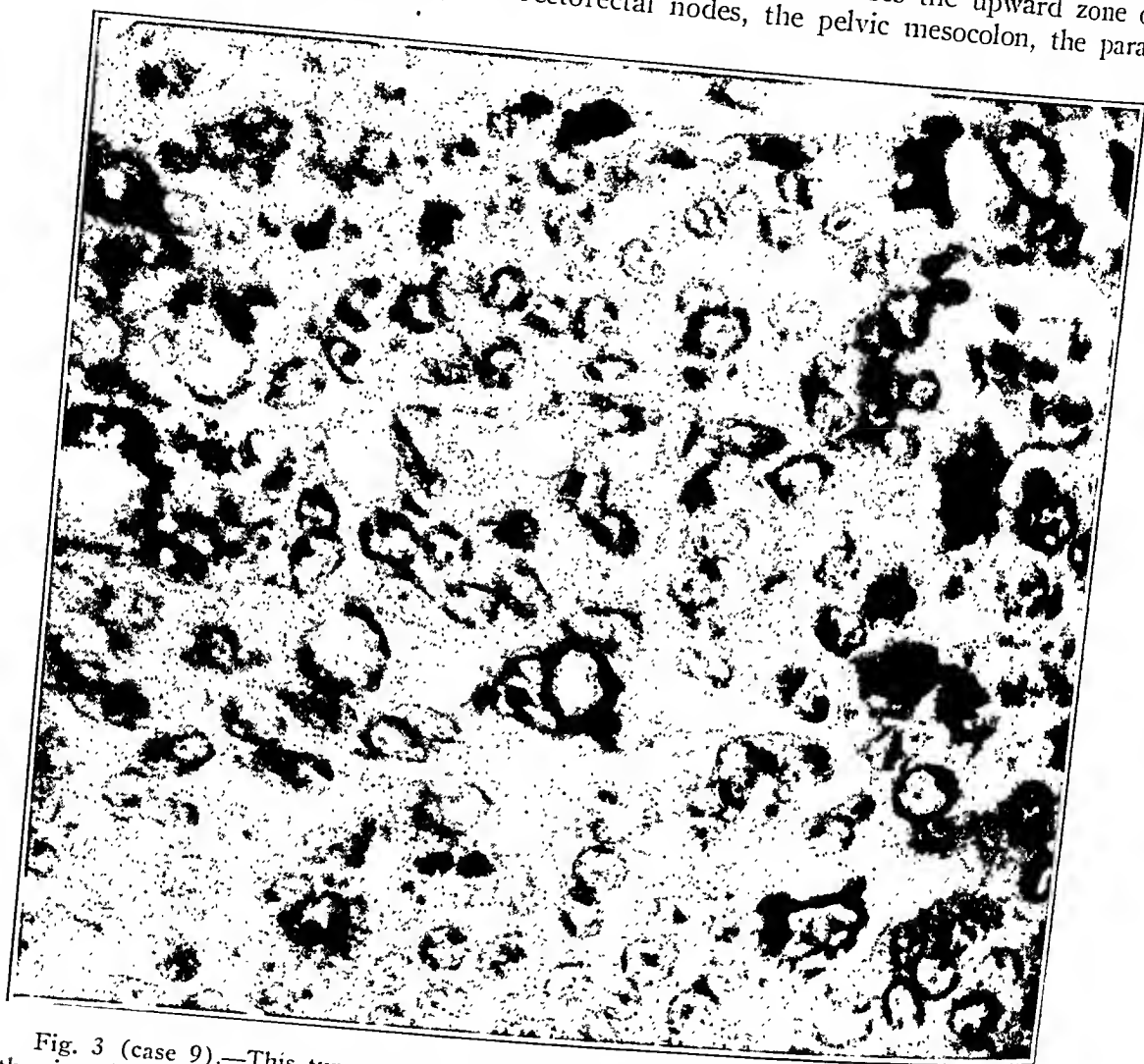


Fig. 3 (case 9).—This tumor was located in the rectosigmoid. Considerable variation in the size, shape and appearance of the cells is seen. Tumor giant cells are present, and cells in various stages of mitosis are plentiful. Another section of this tumor showed invasion of blood vessels. The patient is living and well three years and four months following an abdominoperineal resection. The tumor was classed as grade 3.

colic nodes, the nodes about the bifurcation of the left common iliac artery and the aortic nodes, showed no involvement.

The presence of metastatic carcinoma involving the inguinal nodes was noted in 4 of the 27 cases reported by Keyes. Inguinal metastases are to be anticipated, since the anal skin up to the mucocutaneous junction is drained by lymphatics which lead to the innermost group of inguinal nodes. Lymphatics from the anus pass forward on each side in the fold between the thigh and the perineum to reach

the inguinal nodes of that side.<sup>9</sup> This site of possible metastasis should always be kept in mind and the inguinal nodes examined in every case of carcinoma of the anus. The exact location of a tumor has much to do with the path its metastases take. Tumors below the mucocutaneous junction metastasize to the inguinal nodes most frequently, while tumors above the junction much less commonly involve these nodes but seem to prefer the perirectal tissues.

The only figures of significance relating to the incidence of metastases are those of Keyes.<sup>2a</sup> Metastases occurred in 19, or 70 per cent, of his 27 cases. The impor-



Fig. 4 (case 10).—In the center of the section, tumor cells can be clearly seen in a blood vessel. On the basis of this and other sections the tumor was classed as grade 3. An abdomino-perineal resection was performed, but the tumor had invaded the prostate gland and could not be entirely eradicated. The patient has survived six months and has shown no evidence of recurrence up to date.

tance of these figures cannot be too strongly emphasized. This high occurrence rate of epidermoid metastasis makes it obligatory for the physician to regard every patient with epidermoid carcinoma of the anus as having metastases in one or more

9. Nesselrod, J. P.: Demonstration of Genito-Ano-Rectal Lymphatics, *Tr. Am. Proct. Soc.* 36:85-90, 1935.

of the regions listed, no matter what may be his conclusions regarding the primary tumor. We feel certain that the failure to recognize these possibilities and the consequent failure to provide for them in the plan of treatment have figured prominently among the causes of poor end results.

Many investigators<sup>10</sup> have pointed out that metastases from squamous cell carcinoma of the anus do not involve the upward zone of spread of Miles. Keyes found that the highest metastasis in his series was located less than 14 cm. above the anus and that this was from a lesion which extended 8 cm. up into the rectum. In 1 of our 10 cases (case 4) a metastatic tumor was noted involving a lymph node 8 cm. above the anus. The primary lesion in this case extended up into the rectum. These sites of metastasis are much higher than usual and, for practical purposes, may be assumed to represent the extremes of upward extension. Anatomically, the upper extreme may be considered to lie somewhat above the level of the pelvic peritoneal reflection off the rectum. This has an important bearing on surgical treatment and will be referred to again in that connection. The nodes most frequently involved are those in the ischiorectal tissues immediately surrounding the anal canal.

These opinions and observations relating to metastases are in agreement with those expressed by most writers on this subject. There is some difference of opinion as to whether metastases occur early or late. In 1 of the cases of our series, inguinal metastases appeared five months after rectal resection. On the other hand, in 2 of the cases reported by Keyes,<sup>2a</sup> inguinal metastases were noted four years after surgical removal of the primary tumor. Fischel<sup>11</sup> noted inguinal metastasis in 2 of his cases after rectal resection. These metastases appeared two years and four years respectively after surgical treatment. There is no way of determining when the inguinal implantation actually occurred in these cases, but it is probable that they were present for some time before they became noticeable. This viewpoint is supported by the studies of Collier<sup>12</sup> and his associates, who demonstrated the presence of metastatic carcinoma in nodes which were not clinically enlarged and which in many instances were so small that they could be demonstrated only through treatment of the tissues by a special clearing process. According, clinical estimates as to when metastases are most likely to occur and as to whether or not they have occurred are no better than guesses. It follows, then, that to cover the common eventualities one must deal with every case as though metastases had already occurred, whether or not they are present clinically.

Enlargement of the inguinal nodes may be on an inflammatory basis and does not necessarily indicate a metastatic tumor. In several instances,<sup>2a</sup> inguinal dissections have been performed for enlarged inguinal nodes associated with carcinoma of the anus and the dissected nodes have been found to show only inflammatory changes. This possibility is mentioned only for its interest and of course should not be allowed to influence one's decision for or against inguinal dissection.

Metastatic involvement of the inguinal glands may occur in patients with adenocarcinoma of the rectum or colon. We have observed this in 2 patients with cancer of the rectum, in 1 with cancer of the rectosigmoid and in a fourth with cancer of the hepatic flexure of the colon. Both of the patients with rectal cancer had extensive involvement of the regional lymph nodes in the zone of upward spread, which suggests that the lateral and downward spread was the result of blocked lymphatics above. The malignant extension in the other 2 patients was

10. Raiford.<sup>1c</sup> Keyes.<sup>2a</sup>

11. Fischel, E.: *Cancer of the Rectum*, J. Missouri M. A. **33**:419-423 (Nov.) 1936.

12. Collier, F. A.; Kay, E. B., and MacIntyre, R. S.: *Regional Lymphatic Metastasis of Carcinoma of the Rectum*, *Surgery* **8**:294-311 (Aug.) 1940.

by means of the peritoneum, since gravity metastases were found in the lower part of the abdomen extending into the inguinal canal and to the inguinal lymph nodes. Three of these patients are dead, and the fourth is living, twenty-eight months after a Miles resection, with intraperitoneal and inguinal metastases.

Of the 10 cases of epidermoid carcinoma which we are reporting, metastases were demonstrable in 2 through the pathologic examination of tissue removed at operation. In 1 of these 2 instances (case 4) there were 9 normal lymph nodes and 1 containing tumor tissue, the tumor-laden node being located 8 cm. above the anus. The primary tumor here was situated in the anal canal and the lowest portion of the rectum. A Lahey two stage abdominoperineal resection was performed, but the tumor recurred in the posterior wound and was eventually fatal. In the other case (case 5) 3 of 7 lymph nodes showed metastasis, these nodes being situated in the perirectal fatty tissue. The patient died eight days after operation. Autopsy was not permitted in either of these cases. In the first of these 2 cases the tumor contained areas classed as grade 1 and other areas classed as grade 2. In the second case the tumor was classed as grade 1. Both the tumors were large and appeared to be growths of fairly long standing.

Involvement of inguinal nodes was not observed in any of our 10 cases when the patients were first examined at the Lahey Clinic. However, 1 of the patients (case 6), on whom a Miles abdominoperineal resection was performed five months ago, has just returned to the clinic complaining of masses in both groins. After excision one of these masses was found to be carcinomatous, while the other showed only inflammatory changes. In this case the primary tumor, showing characteristics of both grade 2 and grade 3, originated at the mucocutaneous junction and was protruding from the anus at the time of the patient's first examination. It did not extend up into the rectum. To date in none of the remaining cases has there been evidence of inguinal metastases, but it is a distinct possibility that such metastases may yet make their appearance.

Abdominal exploration was performed in 8 of the 10 cases and failed to reveal abdominal metastases in any instance.

In the most recent of our cases (case 10) the tumor was found to have invaded the prostatic capsule so that complete removal was impossible. No final statistics can be given as regards metastases, since in only 2 of our 10 cases has five years or more elapsed since the date of treatment.

*Treatment.*—Epidermoid carcinoma of the anus is fairly radiosensitive, as is the same type of tumor when it occurs elsewhere in the body. Some writers<sup>13</sup> have advocated therapy by irradiation alone as offering the best chance of cure. Usually radium in some form has been preferred for the control of the primary lesion and inguinal nodes. Interstitial radium applied as radon needles appears to be very effective in producing regression of the primary tumor. Radium element may be administered to the primary growth by means of a perineal applicator or a proctostat. The inguinal nodes have been most frequently treated with roentgen rays, but radium applicators and radon seed have been used as well. Most workers have administered roentgen therapy to the pelvis in addition to the aforementioned measures.

Dosages and methods have varied so with individual investigators that we shall not attempt to present further details. For a description of specific dosages

13. (a) Bacon, H. E.: The Present Status of Radiation Therapy in Carcinoma of the Anus, Rectum and Sigmoid Colon, *Am. J. Digest. Dis. & Nutrition* 3:255-257 (June) 1936. (b) Footnote 7.

and technics, the reader is referred to the paper by Bacon,<sup>13a</sup> in which the methods used by several of the better known investigators are presented.

The immediate response to radiation treatment may be noted in many cases, and cure may be obtained in some cases by this means alone.

Bensaude and his associates<sup>2b</sup> have reported the results in 20 patients treated with interstitially inserted radon needles plus radium administered by a perineal applicator. No details of the treatment of individual patients is given. Of the 20 patients, 1 was free of disease after ten years, 3 after five years, 2 after two years, 1 after one and one-half years and 1 after one year following treatment. In other words, 8 patients were free of disease but only 4 of these, or 16 per cent of the whole group, had been followed as long as five years. On the other hand, in 8 patients tumor recurred at the original site or in the nearby lymph nodes. In the remaining 4 patients the primary lesions failed to regress under irradiation treatment. Therefore, although statistics are incomplete so far as regards five year survivals, it is fairly certain that at least 12 of the 20, or 60 per cent of the patients, were doomed, either through recurrence of disease or through failure of response of the lesion to initial treatment.

The failure of epidermoid carcinoma of the anus to respond to irradiation in some instances has been noted by others.<sup>5</sup> In 11 of the cases of Buie and Brust,<sup>1b</sup> irradiation was the only method employed for destruction of the tumor. In 5 of the patients metastases had developed; 5 were free of disease, and 1 was being treated palliatively. None of them had been followed five years.

In the cases reported in the literature the greatest proportion of the patients who have been subjected to irradiation have been followed for from a few months up to about four years. We can draw no final conclusions from these cases, since it has been repeatedly observed that fatal metastases may not make their appearance until the third to the fifth year following treatment. However, negative conclusions can be reached, for in almost half of the cases in which irradiation was used recurrences had taken place within the first year or two following treatment. Keyes<sup>2a</sup> has noted that inguinal metastases are not amenable to cure by irradiation or by surgical operation, once they are clinically present.

The discomfort incident to irradiation is severe in most cases.

From these considerations we must conclude that present methods of radiotherapy result in eradication of tumor in appreciably less than 50 per cent of the cases. This evaluation may have to be revised pending the appearance in the literature of more complete reports.

Some have favored complete reliance on surgical removal, except in the event of inoperable lesions or inoperable recurrences. Those holding this opinion have favored some form of rectal resection plus dissection of the inguinal lymph nodes. The type of rectal resection advised has ranged from the abdominoperineal operation of Miles to a posterior excision with the formation of a perineal colostomy opening.

Keyes noted recurrences in 11 of his 27 cases, surgical methods having been employed. These recurrent growths appeared either in the posterior wound site or in the groin. The only exception was in 1 case with questionable metastases to the lungs. Six patients of the group were free of disease when last examined. The follow-up period varied from about one and a half to three and a half years. Three of these 6 patients had inguinal dissections in addition to the treatment directed at the primary lesion itself. These inguinal dissections were of a prophylactic nature. It will be extremely interesting to note what happens to these patients. No conclusions can be drawn as yet. Keyes did not mention what type of procedures were employed in the cases in which recurrences developed.

Four of the patients in a series of 43 reported on by Buie and Brust<sup>1b</sup> were alive after five years. In 1 case local destruction of the lesion with cautery was carried out and a colostomy was done; in another local excision plus roentgen therapy was used and in the remaining 2 posterior excision of the rectum was done. Of the 43 patients, 14 were treated by operation alone. Nine of the 14 were free of disease from five months to seven years. Three patients died, and 2 were not followed.

All of the 10 patients comprising the Lahey Clinic group were treated by operation alone. One patient is living and well ten years and another six years after treatment, both having had colostomy and posterior rectal resection. Three patients died. One of these (case 3) had had a loop colostomy and refused further treatment of any sort. There was 1 postoperative death (case 5) after a second stage Lahey resection. The third death (case 4) was due to recurrence in the wound. A two stage Lahey resection had been done in this instance. Recurrence in the site of the posterior wound led to resection of the coccyx, but a second recurrence was fatal.

One patient (case 6), already referred to, is in the hospital now with incurable inguinal metastases which appeared five months after a Miles abdominoperineal resection was performed.

The remaining 4 patients are well to date, having survived free of disease for from six months to three years and four months. To summarize our present results, 6 patients are well after from six months to ten years and a seventh is living with extensive metastases to the groin.

It is obvious that these surgical results do not lend themselves to final evaluation. However, several important conclusions are evident. In general, the operative procedures performed in the past and at present are not extensive enough to eradicate all tumor tissue in the average case. Such an operation as excision of the lesion with the cautery or posterior excision of the rectum will yield cures in the earliest, most favorable cases but when applied to average cases will push the number of recurrences up to a formidable figure. We may further conclude that metastases when clinically present cannot be eradicated by a surgical operation. Important is the fact that almost all observers to date have remarked on the rarity of intra-abdominal metastases. Abdominal exploration was performed in 8 of our 10 cases, and gave negative results in every instance. Summarizing results to date, operation alone has been more effective than irradiation alone. These results point toward radical operation as the type of therapy offering the best prognosis.

Therapeutic combinations of irradiation and surgical intervention have been widely employed. Raiford<sup>1c</sup> suggested external irradiation followed by radical surgical intervention. Hayden<sup>1a</sup> advised surgical resection of the rectum followed by roentgen therapy to the inguinal lymph nodes. The possible combinations are numerous, as is shown by the variation in the treatment administered in the cases reported by Buie and Brust.<sup>1b</sup> This multiplicity of methods makes any attempt at evaluation worthless. Buie and Brust<sup>1b</sup> concluded that either surgical treatment or irradiation is satisfactory if applied with sufficient aggressiveness.

Hankins<sup>1f</sup> suggested that surgical treatment is best in dealing with tumors of grades 1 and 2 but that irradiation is more effective against grades 3 and 4. Kerr<sup>2c</sup> has clearly shown what we would naturally expect, namely, that the mortality rate is much higher with tumors of grades 3 and 4 than with those of grades 1 and 2. The former tumors metastasize earlier and more widely. However, metastases are common with tumors of lower grade malignancy; hence one has no right to employ a more conservative type of surgical treatment for tumors of these grades. Nor does it seem reasonable to abandon operation in favor of irradiation for tumors of grades 3 and 4 because their malignancy is greater and their mortality higher. Few of

these can be cured by irradiation, while a considerable number are amenable to radical surgical treatment. We believe that grading of anal carcinoma is valuable in formulating a prognosis. But when one uses it as a guide to determine the method of therapy to be employed one is attempting to draw lines where no definite lines can be drawn. We believe radical surgical treatment offers the patient the best chance of cure, regardless of the histologic gradation of his tumor, and we believe that all patients with operable lesions are entitled to this type of treatment.

In attempting to formulate such a plan of surgical treatment it is necessary first to define the potential extent of the pathologic process to be eradicated. The primary tumor must be dealt with, including the surrounding tissues which may be involved by direct extension. These tissues include the anal skin and a wide area of perianal skin, the anal sphincter, the rectum, the ischiorectal fat, the levator ani muscles and usually the posterior wall of the vagina. Possible sites of lymphatic metastases must be taken into account. These include the lymph nodes in the ischiorectal fat and the levator ani muscles, the rectorectal nodes, the mesocolic nodes and any nodes lying under the peritoneum of the pelvic floor. Also, one must include the nodes of both inguinal regions and the iliac glands.

Removal of the tissues just enumerated will require two operative procedures, an abdominoperineal resection and a bilateral inguinal dissection. The method of abdominoperineal resection described by Miles is adequate for the treatment of the lesion itself and the regional metastases which may be present. Any one of several other methods are also adequate, provided they are as radical as the procedure of Miles. A permanent abdominal colostomy opening should be made in all cases. The inguinal dissection should include both the femoral, inguinal and iliac nodes along with the surrounding fatty tissue. No effort is made to remove the lymphatic vessels leading from the anus to the groin.

Both these procedures should be performed in every case of an operable tumor in which cure is possible and feasible. Deviations from this approach should be limited strictly to cases in which the lesion is obviously beyond cure and the only goal is palliative relief. We have no hesitancy in performing inguinal dissection when the glands are known to be involved for the relief of pain or to avoid ulceration.

The inguinal dissection should follow the abdominoperineal operation, with at least seven days intervening. The dissection will be a prophylactic procedure in most instances but is nevertheless essential in every case. Enlarged inguinal nodes are no contraindication to the dissection, since the nodes may be inflammatory and it is only through such a dissection that the presence or absence of metastases to the groin can be established.

Contraindications to operation are few. A tumor is considered inoperable only if it has obviously invaded some structure, such as the prostate or broad ligaments, from which it cannot be resected. Rarely will a patient be found who is too poor an operative risk to be subjected to a surgical procedure.

We feel that irradiation should be reserved for patients who, for one of the foregoing reasons, cannot be operated on and for patients having a nonresectable recurrent tumor. In cases of operable cancer irradiation may be used as an adjunct to but not as a substitute for radical operation. We have had no experience with preoperative or postoperative irradiation.

#### COMMENT

As has been brought out, the foregoing discussion deals only with squamous cell, or epidermoid, carcinoma. The clinical distinctions between this type of anal tumor and other types, such as basal cell carcinoma and adenocarcinoma, are not as



great as the histologic differences would imply. All these tumors show a tendency to metastasize to the lymph nodes in the groin as well as to the nodes about the anus and the lower part of the rectum. Adenocarcinoma, as Keyes pointed out, differs from epidermoid carcinoma in that it fairly often spreads to the lymph nodes of the sigmoid mesocolon and to the liver. Basal cell carcinoma, on the other hand, remains localized as a rule and has a much lower incidence of metastases than does squamous cell carcinoma. Instances of metastases to the groin from an anal basal cell tumor have been reported, however.

We are watching with particular interest the patient whose lesion was located in the rectosigmoid (case 9). This patient is free of disease, having had a two stage Lahey resection of the rectum three years and four months ago. The tumor was histologically of grade 3 and showed invasion of the blood vessels.

Neither surgical treatment nor irradiation has been radical enough in the past. End results following both types of therapy would no doubt be much improved if radical methods were instituted and standardized. We feel that five year survival rates should rise from 60 per cent to 80 per cent with the acceptance of radical operation as the method of choice in every case. The procedure suggested is the minimum which will give satisfactory results in the greatest number of cases. The rectal resection should include resection of the coccyx, posterior vaginal wall or other resectable tissues which happen to show involvement. Especial pains should be taken to excise a wide area of perianal skin, as was advocated by Miles. It is hoped that the practice of local excision for so-called favorable lesions will be abandoned. These favorable lesions will give most favorable results if treated radically, whereas one is courting recurrence and a fatality in over 50 per cent of the cases if one employs local excision alone.

Prophylactic inguinal dissection was proposed and carried out by Keyes. We feel that the idea is sound, especially since the outlook is hopeless once the nodes in the groin are clinically involved. Final opinion of this procedure must wait.

The operative mortality over the past three years in cases of all types of lesions of the rectosigmoid, rectum and anus in which the Miles abdominoperineal resection has been used at the Lahey Clinic has been 7 per cent. No mortality statistics are available for radical inguinal dissections in patients having epidermoid carcinoma of the anus. The combined operative mortality rates of these two procedures should not exceed 10 per cent. One death in our group of 10 cases was an operative death.

#### SUMMARY AND CONCLUSIONS

Treatment of epidermoid carcinoma of the anal region has been attended by poor results in the past, regardless of the method employed.

Ten cases of epidermoid carcinoma have been presented. In 9 of these the growth was anal, while in 1 the tumor occurred in the rectosigmoid.

Microscopic study of all anal and rectal lesions is urged, in order that carcinoma may never be overlooked when present.

Various methods of therapy have been reviewed. It is our conclusion that radical operation offers the best prognosis. A surgical approach consisting of a Miles abdominoperineal resection and a radical inguinal dissection is advocated for every operable growth. This recommendation is based on a detailed pathologic and clinical study. Irradiation is indicated for inoperable lesions and for recurrences following operation.



# DERMOID AND EPIDERMOID TUMORS (CHOLESTEATOMAS) OF THE CENTRAL NERVOUS SYSTEM

## REPORT OF TWENTY-THREE CASES

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Publications appearing from time to time since Verattus<sup>1</sup> first described a dermoid variety of tumor in 1745 have told so well the story of neoplasms of this type that it has become familiar to those interested in the subject. Because of confusion in nomenclature and controversies regarding pathology, it seems essential to reconsider some of the earlier works in this field. We trust that it may crystallize concepts concerning these unusual neoplasms.

Most articles dealing with the history of dermoids and epidermoids have referred to the excellent review by Bostroem<sup>2</sup> in 1897. According to Mahoney<sup>3</sup> the first communication regarding an epidermoid came from Pinson,<sup>4</sup> an artist in the School of Medicine of Paris, in the year 1807. He prepared a wax model of such a tumor located in the region of the cerebellum and fourth ventricle and described its grayish white interior and silvery white capsule. Dupuytren included the model in the school collection, and Chazel made a beautiful reproduction of it for Cruveilhier's Atlas. Several authors, including Horrax<sup>5</sup> and Critchley and Ferguson,<sup>6</sup> stated that Duméril<sup>7</sup> demonstrated this model and reported the case before the Société de Médecine. According to Critchley and Ferguson, Cruveilhier, referring to this case twenty years later, stated it had occurred in Dupuytren's service at the Hôtel-Dieu about 1803-1804.

Epidermoids were next described by Rudolphi<sup>8</sup> in 1813, by Parent-Duchatelet and Martinet<sup>9</sup> in 1821, and by Le Prestre<sup>10</sup> in 1828. The following year, in his famous "Anatomie Pathologique," Cruveilhier<sup>11</sup> fully described the tumor of Pinson and Duméril, which, because of its highly refractile and nodular surface, he termed *tumeur perlée*. At the same time he reported a parapituitary epidermoid

1. Verattus, M. V.: De Bononiensi scientiarum et artium instituto atque academia commentarii, Bononiae, 1745, vol. 2, pt. 1, p. 184.

2. Bostroem, E.: Ueber die pialen Epidermoide, Dermoiden und Lipome und duralen Dermoiden, Centralbl. f. allg. Path. u. path. Anat. 8:1, 1897.

3. Mahoney, W.: Die Epidermoide des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. 155:416, 1936.

4. Pinson: Bull. École de méd. de Paris 2:32, 1807; cited by Mahoney.<sup>3</sup>

5. Horrax, G.: A Consideration of the Dermal Versus the Epidermal Cholesteatomas Having Their Attachment in the Cerebral Envelopes, Arch. Neurol. & Psychiat. 8:265 (Sept.) 1922.

6. Critchley, M., and Ferguson, F. R.: The Cerebrospinal Epidermoids (Cholesteatomata), Brain 51:334, 1928.

7. Duméril, A. M. C.: Bull. Fac. de méd. de Paris 1:32, 1807; cited by Mahoney.<sup>3</sup>

8. Rudolphi, K. A.: Arch. f. med. Erfahrung 1:508, 1813.

9. Parent-Duchatelet, A. J. B., and Martinet, L. M.: Recherches sur l'inflammation de l'arachnoïde cérébrale et spinale, Paris, Crevot, 1821, p. 439.

10. Le Prestre, F.: Tumeur adipociriforme développée dans le mésocéphale, Arch. gén. de méd. 18:5, 1828.

11. Cruveilhier, J.: Anatomie pathologique du corps humain, Paris, J. B. Baillière, 1829, vol. 1, book 2, plate 6 and p. 341.

in an 18 year old girl. He was the first to describe completely the origin and pathologic character of these tumors. In 1834 Peyrot<sup>12</sup> reported an epidermoid just posterior to the pons and adherent to the cerebellum, which he believed to be identical in character with that already described by Cruveilhier.

In 1838 Johannes Müller,<sup>13</sup> noting the association of cholesterol crystals with these tumors, introduced the name "cholesteatoma." He gave a complete gross and microscopic description of 3 such neoplasms, one of which was the first diploic epidermoid to be described. Virchow,<sup>14</sup> studying 4 cases in 1854, suggested a return to the name of pearly tumor. He felt "cholesteatoma" was a misnomer because cholesterol was neither an essential nor a constant finding in these tumors.

Esmarch<sup>15</sup> in 1856 and Bailey<sup>16</sup> in 1920 gave a brief account of what appears to have been the first surgical treatment of an epidermoid, namely, a diploic tumor of the frontal bone.

Eventually it was felt that "pearly tumor" described only a limited class of cholesteatomas, merely implying that some tumors of this general group had a pearly luster because of the highly refractile quality of their covering. The non-hair-containing epidermoid variety revealed this peculiarity most strikingly, the pearly sheen depending on whether only the upper, and not the lower, or dermal, layer was included in the tissue of origin. Bostroem<sup>2</sup> and Horrax<sup>5</sup> have, however, reported cases in which the cholesteatoma gave the characteristic appearance of pearly tumor and yet contained hair, showing that this highly refractile covering was not confined to the non-hair-containing variety. Such findings emphasize the almost certain general relationship of these tumors. As Kato<sup>17</sup> has pointed out, the occasional reports of certain intracranial teratomas show that the deeper layers may be involved or the cell inclusions may have further potentiality.

Bostroem<sup>2</sup> in 1897 described them as "pial epidermoids and dermoids, and dural dermoids," because he felt their supporting tissue was thus best represented. His opinion, however, remains controversial, and the term most frequently associated with this variety of tumor continues to be "cholesteatoma." Horrax<sup>5</sup> modified this to "meningeal cholesteatoma," believing this eliminated the group of tumors containing cholesterol crystals which arise from pituitary rests. Such a term eliminated confusion with the cholesteatomas of the middle ear, which do not have primary meningeal attachment.

Critchley and Ferguson<sup>6</sup> expressed the opinion that "epidermoid" was more suitable than other terms employed, since it was brief and accurate and conveyed the idea of the epithelial nature of the growth. They emphasized the fact that "epidermoid" could be readily used in contrast to "dermoid" tumors of analogous origin but containing elements other than mere epidermal structure. In 1937 Munro and Wegner<sup>18</sup> divided the tumors into "primary cranial and intracranial epidermoids and dermoids," believing that the concept was thus made more exact. From recent publications it is becoming increasingly evident that the terms "dermoid" and "epidermoid" are most frequently used in describing these neoplasms.

12. Peyrot, M.: Tremblement mercuriel. *Sudamina. Tumeur comprimant le cervelet*, Arch. gén. de méd. 4:620, 1834.

13. Müller, J.: Ueber den feineren Bau und die Formen der krankhaften Geschwülste, Berlin, G. Reimer, 1838, vol. 1, p. 50.

14. Virchow, R.: Ueber Perlgeschwülste. *Virchows Arch. f. path. Anat.* 8:371, 1854.

15. Esmarch, F.: Cholesteatom in Stirnbein. *Virchows Arch. f. path. Anat.* 10:307, 1856.

16. Bailey, P.: Cruveilhier's "Tumeurs Perlées," *Surg., Gynec. & Obst.* 31:390, 1920.

17. Kato, T.: Ein kasuistischer Beitrag zur Kenntnis von teratoiden Geschwülsten in Kleinbrückenwinkel. *Jahrb. f. Psychiat. u. Neurol.* 35:43, 1914.

18. Munro, D., and Wegner, W.: Primary Cranial and Intracranial Epidermoids and Dermoids, *New England J. Med.* 216:273, 1937.

## INCIDENCE

According to earlier statistics, Tooth<sup>19</sup> found but 1 cholesteatoma in a series of 258 cerebral tumors, and Bernhardt<sup>20</sup> 1 in 487. The dermoid variety has been described less frequently than the epidermoid. In 1922 Horrax,<sup>2</sup> adding 3 more to those already reported in the literature, brought the total number of cases to 26. Bailey,<sup>10</sup> on the other hand, had accounted for 62 epidermoids in 1920, making that type of cholesteatoma appear about twice as common. Horrax<sup>2</sup> observed, however, that of 750 verified intracranial tumors in the Brigham series, 3 tumors each of the dermoid and of the epidermoid variety occurred, either type thus representing 0.4 per cent of all intracranial growths.

In 1936 Love and Kernohan<sup>21</sup> expressed the opinion that fewer than 100 epidermoids had been described at operation or necropsy. In the same year Mahoney,<sup>3</sup> on the other hand, in an extensive review of the literature, was able to collect 142 cases. Since then numerous individual reports have appeared. In 1937 Munro and Wegner<sup>18</sup> described a diploic epidermoid, an intracranial dermoid and an intracranial epidermoid. In 1938 Askenasy<sup>22</sup> reported 5 intracranial epidermoids and 1 spinal epidermoid. In 1939 Alpers<sup>23</sup> added 1 diploic epidermoid and 7 intracranial epidermoids. Later in the same year King<sup>24</sup> reported 1 intraspinal epidermoid, 3 intracranial epidermoids and 4 diploic epidermoids. In contrast to this number of epidermoids, Brock and Klenke,<sup>25</sup> in a review published in 1931, were able to collect only 39 cases of intracranial dermoids. Kornfeld<sup>26</sup> in 1930 brought this number to 48, and Courville and Kimball<sup>27</sup> in 1936, to 56.

The series here reported includes 23 cases, 11 of which are instances of diploic, or cranial, epidermoid. Two of the cases, both of dermoid, were reported previously by one of us (C. W. R.). The first was a case of intracranial dermoid cyst of the left temporal region reported in 1925, and the second an instance of dermoid cyst of the inferior cerebellar vermis reported in 1936. Our series represents cases of tumors of this type observed in patients admitted to the neurosurgical service or discovered on postmortem examination at the Los Angeles County General Hospital, as well as cases of such neoplasms studied in private practice. At present, as far as we know, fewer than 200 epidermoids of the central nervous system have been reported.

## REPORT OF CASES

## A. DIPLOIC OR CRANIAL EPIDERMIDS

CASE 1.—*Diploic epidermoid of the right frontal region previously operated on as a sebaceous cyst; complete removal and recovery.*

19. Tooth, H. T.: The Treatment of Tumours of the Brain, and the Indications for Operation, Tr. Internat. Cong. Med., London (sect. 11, Neuropath.), 1913, p. 252.

20. Bernhardt, M.: Beiträge zur Symptomatologie und Diagnostik der Hirngeschwülste, Berlin, A. Hirschwald, 1881.

21. Love, J. G., and Kernohan, J. W.: Dermoid and Epidermoid Tumors (Cholesteatomas) of the Central Nervous System, J. A. M. A. **107**:1876 (Dec. 5) 1936.

22. Askenasy, H.: Les tumeurs perlées du névraxe, Encéphale **1**:209, 1938.

23. Alpers, B. J.: Cerebral Epidermoids (Cholesteatomas), Am. J. Surg. **43**:55, 1939.

24. King, J. E. J.: Extradural Diploic and Intradural Epidermoid Tumors (Cholesteatoma), Ann. Surg. **109**:649, 1939.

25. Brock, S., and Klenke, D. A.: A Case of Dermoid Overlying the Cerebellar Vermis: A Review of the Literature on Intracranial Dermoids, Bull. Neurol. Inst. New York **1**:328, 1931.

26. Kornfeld, M.: Ueber intrakranielle dysontogenetische geschwülstartig Bildung an der Hand eines pialen, sekundär stark veränderten Dermoids am Kleinhirn, Virchows Arch. f. path. Anat. **278**:165, 1930.

27. Courville, C. B., and Kimball, T. S.: Subpial Dermoid Cyst of Inferior Cerebellar Vermis, Bull. Los Angeles Neurol. Soc. **1**:84, 1936.

In 1926 a 13 year old boy first noticed a small swelling in the right frontal region, which gradually increased in size until it became about as large as a walnut. In September 1929 he was operated on for a supposed sebaceous cyst of the scalp. At this time, however, it was discovered that the cyst extended through the inner table of the skull. A considerable amount of cheesy material was removed, and the wound was closed without drainage. After healing by first intention the cyst subsequently refilled, and the wound broke down, discharging a thin, brownish fluid which contained the same sebaceous material.

During the months following the patient complained of gradually increasing headache, unassociated with nausea or vomiting. On Feb. 6, 1930 he accidentally struck his head and immediately complained of a severe headache and vomited. That evening his temperature rose to 104.5 F. The following morning he complained of severe headache and pain in the back of the neck and vomited frequently.

*Examination.*—The patient was vomiting and irrational. His neck was stiff, and the Kernig and Babinski signs were present bilaterally. It was believed the patient had an epidermoid cyst in the right frontal region, which, having become infected, ruptured when he struck his head the day previous. Roentgenograms of the skull showed a round, smooth, punched-out area which appeared old. On subsequent examination the characteristics of a diploic epidermoid (fig. 1) were noted. Lumbar puncture yielded a cloudy fluid containing 4,140 cells.

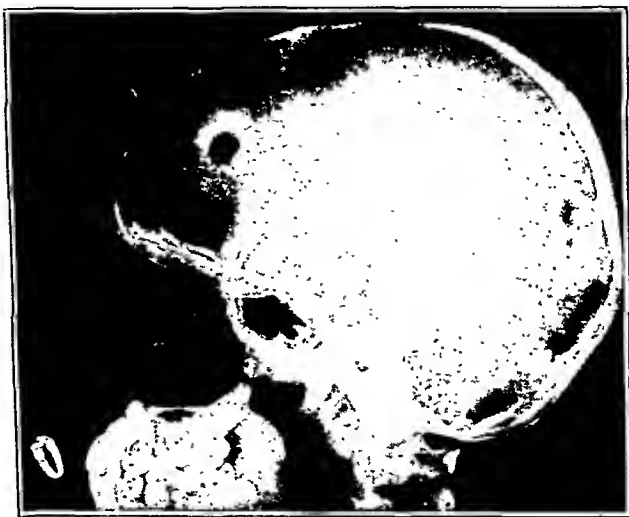


Fig. 1 (case 1).—Roentgenogram of right lateral view of the skull showing the defect in the right frontal region characteristic of a diploic epidermoid.

The globulin content was considerably increased. A Gram stain revealed numerous polymorphonuclear leukocytes and rarely gram-positive cocci in pairs. There was leukocytosis, the white cell count being 60,700.

Operation on February 8 revealed a grayish, soft mass of tissue resembling cerebral cortex. On tapping, a small amount of brownish fluid containing plaques of caseous-appearing tissue escaped. A cyst 2 cm. in diameter was then removed, along with part of the bone about the osseous defect. No cerebral abscess was present. The patient made an uneventful recovery and left the hospital on February 25. On Jan. 20, 1937 he reported that he was in good health and had had no further trouble.

Unfortunately no pathologic report was obtained, but from the roentgenograms and the gross appearance at operation the diagnosis of diploic epidermoid seemed certain.

*CASE 2.*—*Dermoid cyst in the midline anterior to the anterior fontanel; complete removal and recovery.*

A 5 month old boy was referred because of a small swelling in the midline of the skull anterior to the anterior fontanel. This was noticed shortly after birth. Polydactylism was also present, there being an extra toe on each foot and the remnant of an extra finger on each hand.

*Examination.*—The baby, a well developed boy, weighed 16 pounds (7.3 Kg.). Just in front of the anterior fontanel and directly in the midline was a small swelling, symmetric and domelike, measuring 2 by 2 cm. in diameter and elevated approximately 1 cm. above the surrounding scalp. It was somewhat fluctuant and slightly movable but showed no evidence of inflammation. Roentgenograms of the skull showed a defect in the midline anterior to the anterior fontanel and underlying a soft tissue tumor (fig. 2).

On Jan. 27, 1932, a tumor measuring approximately 2 by 2 cm. was easily dissected out. It was oval, well encapsulated and bound to the top of the longitudinal sinus by fine adhesions. It was not lobulated. The patient's postoperative course was uneventful, and he was discharged from the hospital February 6.

Microscopic sections through the center of the cyst showed the cavity to be filled with a structureless debris. Squamous epithelium lined the cavity, and some keratin existed on the surface of the epithelium. The dermal layer was present, but true papillae of the papillary layer were not seen because of flattening from distention by the contents of the cyst. The reticular layer was present, showing both superficial sebaceous glands and deeper sweat glands with numerous scattered hair follicles. A diagnosis of dermoid cyst was made.



Fig. 2 (case 2).—Cranial defect in the midline anterior to the anterior fontanel at the location of the cranial dermoid.

*CASE 3.*—*Diploic epidermoid to the left of the external occipital protuberance eroding through the outer table of the skull; complete removal and recovery.*

A single woman of 23 years was admitted to the hospital Feb. 7, 1936, complaining of intermittent headaches and ringing in the ears. About a year prior to this admission she had begun to have lapses of memory, which gradually increased in frequency.

She had been seen by one of us (C. W. R.) five years previously, after an automobile accident, when a small swelling was noted in the occiput. Roentgenograms at that time revealed a peculiar defect in the skull in the region of the external occipital protuberance. A crater-like area measuring about 1.5 cm. in diameter, involving only the external table, was noted. It did not appear to be a fracture, but was believed to be the result of an old pathologic process. An epidermoid, however, was not suspected. The neurologic examination gave negative results, and her symptoms were believed to be due to a cerebral concussion.

*Examination.*—The patient seemed nervous and emotional. The head showed a soft, slightly cystic, round tumor 2.5 cm. to 3.5 cm. in diameter in the occipital region just to the left of the external occipital protuberance. It seemed attached to the calvarium.

The patient was seen again by one of us (C. W. R.) on February 21, when an oval cystic area in the bone, measuring approximately 4 by 5 cm. in diameter, was found. On palpation a mass about as large as a hen's egg was felt directly over the external occipital protuberance. It had the same peculiar fluctuant quality which had been previously noted. The mass, however, had increased in size. In view of a recent experience with a cholesteatoma in the occipital region (case 6), a similar lesion was suspected. Roentgenograms of the skull

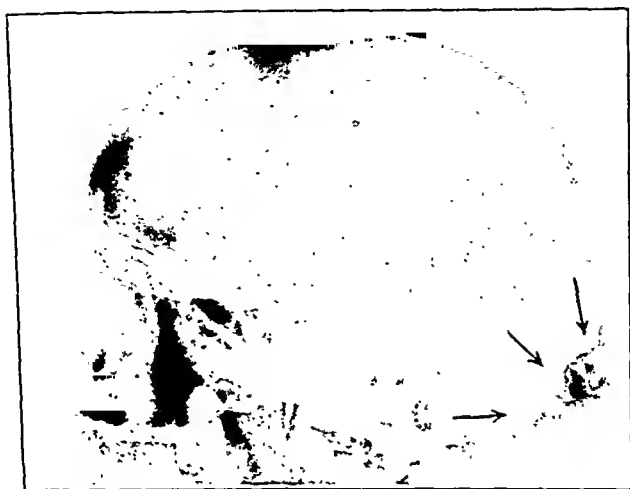


Fig. 3 (case 3).—Lateral roentgenogram of the skull, showing the defect in the occipital region.



Fig. 4 (case 4).—Lateral roentgenogram, showing the diploic epidermoid in the left parietal bone.

taken February 10 revealed a multilocular cystic lesion of the occipital bone extending left from the midline and associated with swelling of the soft tissue. The Wassermann and the Kahn reaction of the blood were reported negative.

On February 24 Dr. G. H. Patterson removed a large epidermoid that had eroded the outer table in the area of the occipital protuberance. The inner table was thinned but intact. The patient made an uneventful recovery, being discharged on March 5. Pathologic examination, both gross and microscopic, revealed a typical epidermoid.

*Comment.*—That diploic epidermoids may be confusing unless one has their identifying roentgenographic characteristics in mind is evidenced by the foregoing case. The occurrence of injury to the head five years previously complicated the diagnosis. A review of the earlier roentgenograms showed them to be characteristic of a diploic epidermoid (fig. 3).

*CASE 4.*—*Diploic epidermoid of the left parietal region; four operations with final complete removal and recovery.*

A girl of 18 years was operated on for a supposed sebaceous cyst of the scalp in the left parietal region by another physician on Oct. 30, 1933. She had been conscious of its presence for five years. During this time it had slowly increased in size. Examination revealed a tumor in the left parietal region about 3 cm. in diameter and 2 cm. above the flush of the scalp. It was movable and did not seem to be attached to the bone.



Fig. 5 (case 4).—Photomicrograph of the diploic epidermoid cyst.

Roentgenograms taken October 23 revealed a circular area about 3 cm. in diameter in the central portion of the left parietal bone, with distention and destruction of the tables (fig. 4). The margins of the destroyed area were sharply outlined, suggesting prolonged pressure. The roentgenograms were typical of a diploic epidermoid.

At operation on October 30 a mass on the scalp in the left midparietal region, 2.5 cm. in diameter and extending through the outer table of the skull, was found. It was intimately connected with the inner table. The cyst was filled with sebaceous material. It was removed and the depression in the skull thoroughly cleansed. The specimen after gross examination was reported as containing 1 Gm. of yellow, flaky sebaceous material. A few pieces were covered on the surface with a thin layer of pearly white substance. A thin, membranous strip of tissue having a smooth, gray inner surface was found. This was believed to be a cyst wall. Although the gross appearance of the tumor was that of an epidermoid, it was considered a sebaceous cyst at the time.

Because of recurrence of the tumor, the patient was reoperated on twice in 1936 at two month intervals. At the fourth and last operation on Aug. 19, 1937, the mass was completely

enucleated, the bone curetted and a portion of the scalp immediately above the mass removed. There has been no recurrence. Microscopic sections of the material revealed a typical epidermoid cyst (fig. 5).

*CASE 5.—Diploic epidermoid of the right frontal region eroding through the outer table of the skull. Complete surgical removal and recovery.*

A Negro woman of 44 years was admitted to the hospital in June 1934, complaining of a swelling in the right frontal region of two years' duration. Questioning revealed that she had first noticed a mass in the right supraorbitofrontal region when she was 8 years of age. By 1932 the mass had increased in size, but it was never painful. Her general health had always been good. The Wassermann reaction of the blood was positive.

*Examination.*—A tumor mass about 6 cm. in diameter was found overlying the right frontal region. It had a soft, cystic consistency at its vertex, but merged with the bony substance below. It was felt that she had a benign cystic tumor of the soft tissues of the right frontal sinus.

Roentgenograms of the skull taken May 29, 1934 were reported as showing large areas of cystic degeneration in the right frontal region which were not distinctive in appearance. Some type of benign tumor mass, not connected with the intracranial structures, was suspected.

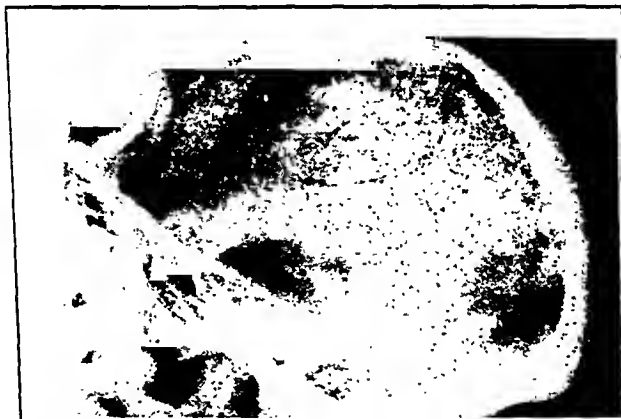


Fig. 6 (case 5).—Lateral roentgenogram of the skull, demonstrating the cranial epidermoid in the right frontal region.

At operation, on July 30, the sebaceous material forming the contents of the cyst, but not the wall of the cyst, was removed. Closure was carried out without drainage. At this time it was not suspected that the tumor was an epidermoid, and the pathologic diagnosis was given as cystic tumor, nonmalignant, type undetermined.

The patient was followed in the outpatient department, where the recurring cyst was aspirated frequently. Eventually the patient was examined in the neurosurgical department. The previous roentgenograms were reviewed and were considered to be characteristic of a diploic or cranial epidermoid (fig. 6). On June 29, 1938 Dr. H. G. Crockett completely removed the tumor and its sac. The tumor had eroded the outer table of the skull, causing a defect about the size of a walnut. The inner table was intact. Convalescence was uneventful. The pathologist reported a small cyst containing flaky white material and numerous other fragments of fibrous tissue. Gross and microscopic examination confirmed the diagnosis of epidermoid cyst.

*CASE 6.—Convulsive seizures for seven years; roentgenograms revealing characteristic findings of an epidermoid; operative removal of a diploic epidermoid cyst; recovery.*

A woman of 54 years gave a history of convulsive seizures occurring once or twice a week during the previous seven years. Consciousness was lost for a few minutes, but no jerking of the extremities was observed. A chewing motion of the jaws accompanied some of the attacks, and occasionally her seizures were preceded by a peculiarly dreamy state in which things seemed far away. There was no history of aphasia or headaches.



*Examination.*—The head revealed no unusual irregularities or tenderness. Except for hypertension (her blood pressure was 215 systolic and 115 diastolic) and a precordial enlargement, the results of general physical examination were essentially negative. The optic disks seemed a little pale, but the remaining neurologic examination showed normal conditions.

Roentgenograms of the skull revealed a discrete shadow measuring about 4.5 by 3.5 cm. in diameter far forward in the right temporal region, which appeared to be in the wall of the temporal and frontal bones. It had the appearance of a diploic epidermoid (fig. 7).

At operation on Sept. 27, 1934 a cyst lying between the inner table of the skull and the dura in the right temporal region was exposed. Its wall was thin, bluish and for the most part friable. Greenish fluid was first liberated, followed by grayish, cheesy, grumous material. Except for its atypical color, it resembled the contents of an epidermoid. The cyst occupied the recess between the temporal and the frontal lobe and dipped down deeply into the sylvian fissure. The bony opening was enlarged to permit removal of the outer wall of the cyst. Except for the portion close to the zygoma, an attempt to dissect the sac from the dura was unsuccessful. The remaining tags of the wall of the cyst were treated with Zenker's solution. The patient made an uneventful recovery.

Dr. R. W. Hammack reported that the specimen consisted of a considerable amount of yellowish, sometimes slightly greenish, soft, structureless material in which there were numerous glistening fine crystals. Some small pieces of tissue represented the lining of the



Fig. 7 (case 6).—Lateral roentgenogram, revealing the diploic epidermoid in the right temporal region.

cavity. Microscopic examination of the soft material revealed numerous cholesterol crystals, but no identifiable epithelial cells. Sections of the tissue consisted of hyaline and necrotic fibrous connective tissue in which were numerous spaces surrounded by cells of inflammatory origin and often by foreign body giant cells. Small spaces lined by cuboidal epithelial cells were found. A diagnosis of epidermoid cyst was made.

*CASE 7.*—Large diploic epidermoid in the midoccipital region; incomplete removal and recovery.

A man of 32 years was referred on Feb. 11, 1933. About September 1934 he first noticed a swelling in the occipital region. During December 1934 his eyes tired easily, and there was noticeable blurring of vision. About this time dizziness on sudden change of position appeared. Increasing dizziness was not accompanied by unsteadiness of gait.

*Examination.*—There was a swelling in the region of the external occipital protuberance, measuring 7 by 6 cm. in diameter and elevated about 2.5 cm. above the surface of the scalp. The swelling consisted of both hard and soft components; the soft area, measuring 3.5 cm. in diameter, was most elevated and showed definite pulsation, which could be seen and felt. No murmur was heard. Bilateral papilledema of about 4 diopters was present, but otherwise the general neurologic examination gave negative results.

Roentgenograms showed a defect in the middle of the occipital bone nearly twice as large as the foramen magnum, the upper margin being practically at the torcula and the lower margin about 1 cm. above the foramen magnum (fig. 8). The lateral view showed some calcification along the outer border. The Wassermann reaction of the blood was negative.

An epidermoid approximately 5 by 7 cm. in diameter was exposed on March 8, 1935. This was filled with grumous material containing large flakes, some resembling pearls. The lining membrane was thin, glistening, pearly and trabeculated. The portion of the membrane which could not be completely removed was treated with Zenker's solution. The osseous defect, measuring about 5 by 6 cm., involved both the inner and the outer table. The patient made an uneventful recovery.



Fig. 8 (case 7).—Posteroanterior view, showing the cranial epidermoid in the occipital region.

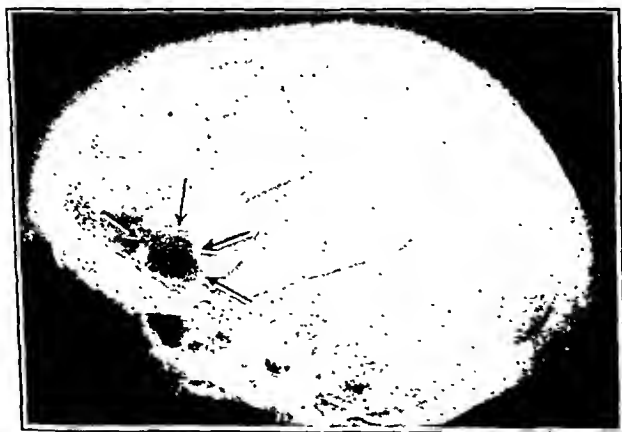


Fig. 9 (case 8).—Lateral view, with the epidermoid defect evident in the left fronto-temporal region.

Dr. R. W. Hammack reported flat epithelial cells and cholesterol crystals. A diagnosis of epidermoid was made.

*CASE 8.—Diploic epidermoid of the left frontal region; operative removal and recovery.*

A woman of 65 years was first seen on Oct. 6, 1936 and complained of a swelling in the left frontotemporal region which was first noticed after she struck her head against a stove about fourteen years previously. The tumor had increased in size during the last six weeks. Convulsions began at 35 and continued at about monthly intervals until three years ago, when they subsided. Considerable headache followed the attacks, and she at times was

unable to speak, although she knew what she wished to say. This patient was right handed and had never had any difficulty with reading or writing. She had taken phenobarbital regularly for the past three years.

*Examination.*—A swelling measuring approximately 4 by 5 cm. in diameter and elevated about 1 cm. above the surrounding scalp was noted in the left frontotemporal region. The scalp was freely movable over the underlying mass and did not seem to be affected. The swelling was neither reddened nor tender. No other unusual irregularities were discovered. Roentgenograms of the skull showed an oval defect in the left frontotemporal region, measuring 3 by 3 cm. in diameter (fig. 9), having the appearance of a diploic epidermoid. The Wassermann reaction of the blood was negative.

The patient was operated on on October 15, when the outer table was opened over the tumor and about 15 cm. of black blood was liberated. The remaining contents consisted of what appeared to be broken-down, degenerated tissue. The inner table was eroded through in some places and very thin in others. As much of the tumor tissue as possible was removed as well as the involved bone. An uneventful recovery was made.

She was last seen on Aug. 2, 1939, having had a convulsion about three weeks previously and a second attack a week later. The area of osseous defect in the left temple remained unchanged. A slight pulsation was obtained on coughing. General physical and neurologic



Fig. 10 (case 9).—Posteroanterior roentgenogram, showing separation of the inner and the outer table by the cranial epidermoid.

examinations gave negative results. Review of the roentgenograms showed them to be characteristic of a diploic epidermoid. Microscopic examination revealed bits of striated muscle, fibrous connective tissue and small spicules of bone. Fibrous connective tissue, in which were many large mononuclear cells with a foamy, granular cytoplasm, was found between the spicules of bone. In other areas a fibrous connective tissue was observed in which were many cleftlike spaces from which crystals, probably cholesterol, had been dissolved. About these were some multinuclear giant cells. No epithelial elements were seen in the tissue. There was no evidence of malignancy. Dr. Angus Wright was of the opinion that the histologic picture was that of an epidermoid growing within bone.

*CASE 9.*—Gradually enlarging tumor of the left parietal region, first noticed at the age of 9 years; operative treatment at the ages of 34 and 36, and again at the age of 44; continued drainage since that time; further removal of a large infected diploic epidermoid July 1937, at the age of 64; with subsequent recurrence and two additional operations; death from bronchopneumonia in April 1939; autopsy.

A 64 year old carpenter had first noticed a swelling, which was thought to be a wen, in the left parietal region at the age of 9 years. At 30 he was struck on the head by a piece of timber. At this time the tumor ruptured, but subsequently healed without treatment.

After this it grew more rapidly, and when the patient was 34 it was the size of an orange. At this time he was operated on at Shenandoah, Iowa; the contents of the tumor were emptied but the capsule was not entirely removed. After a short period of drainage the wound closed. The tumor again increased in size and was reoperated on two years later. Again the wound drained for a short time before closing. After remaining quiescent for a few years, it increased in size slowly. No information was available concerning pathologic observations made in these two procedures.

On Feb. 2, 1917, at the age of 44, he was examined at the Mayo Clinic. He was operated on there, for the third time, on March 10, 1917, by Dr. J. C. Masson, who removed a large quantity of foul, broken-down, sebaceous material. A large cavity, measuring 3 by 2 (7.5 by 5 cm.) inches in diameter, extending through the outer table of the skull in the parietal region was noted. No pathologic report is available. After operation the wound continued to drain. Later the odor from the drainage became offensive. The discharge consisted of a cheesy material together with foul greenish fluid. The wound required frequent dressings, as many as three or four a day in the later years of the patient's life.

About April 1, 1937 inflammation developed over the left side of the scalp. This increased rapidly and was painful. A cellulitis developed involving the entire left side of the head. As the swelling subsided, a residual area of fluctuation high up in the parietal region was noted. An area of bone destruction measuring approximately 10 by 8 cm. in diameter was seen in the roentgenograms at this time. The outer table was principally affected, but in one area the inner table appeared to have been eroded through. At one point in the anteroposterior view separation of the inner and outer tables was seen (fig. 10).

*Examination.*—The entire left side of the scalp was boggy. In the midparietal region was an old sinus tract. A fairly definite osseous defect, measuring approximately 10 by 8 cm. in diameter, could be felt in the skull. Rather high toward the left frontal region there was an area of fluctuation under the scalp. The area of fluctuation was drained April 23, 1937. On July 22, when the left parietal region was reexplored, an abundance of infected granulation tissue was uncovered. The inner table of the skull had been eroded over an area 5 by 5 cm. in diameter. Above this erosion was a mass of pearly white avascular tissue, such as is usually seen in the contents of a cholesteatoma. Surrounding this material was a definite thick sac, apparently lined by epithelium. Above this was an area of osteomyelitis of the skull. The entire mass was dissected out, and the diseased bone was removed by rongeurs. The dura was not ruptured. Anteriorly the cyst had grown between the inner and outer tables of the skull and was separating them. The case was believed to be that of a typical large diploic epidermoid. The history was unusual in that three operations had been performed without complete removal of the tumor.

Dr. A. G. Foord reported epidermoid cyst with extensive chronic inflammatory change. No conclusive evidence of malignancy was discovered, although some portions of the microscopic sections were suggestive.

When the patient was seen Aug. 26, 1937 there was a small discharging sinus with a characteristic odor. It was believed there might be a small area of infected bone beneath. When he was again examined, September 22, the wound was still discharging. Some flaky tissue suggestive of an epidermoid cyst was liberated. It was thought advisable to reexplore the wound. This was done September 24. In several places remnants of the epidermoid cyst were found, and newly forming, cheesy, whitish debris was encountered. The osteomyelitis had advanced toward the midline of the skull. The infected bone and as much of the remaining epidermoid as possible were removed. Suspicious areas were coagulated with the electrocautery, as was the under surface of the scalp. Although it had been believed that all remnants of the sac were removed by the first procedure, this was disproved by the second operation. It was hoped that no subsequent reformation of the cyst would occur, but on this occasion the operator was dubious such would be the case. Dr. A. G. Foord reported epidermoid epithelium with profound hyperkeratosis.

After the second procedure, aphasia and weakness of the right hand developed, which were believed secondary to cauterization of the dura. These symptoms improved steadily, so that on October 14 the patient was able to use the right hand well, although not so well as the left, and at the same time his speech was much improved. He still experienced difficulty in reading. When he was again seen, Jan. 25, 1938, swelling and inflammation of the upper frontal region were present and recurrence of the epidermoid was thought to be evident. Another exploratory operation was performed February 1. The recurrent epitheliomatous growth was removed and all remnants of the growth on the dura cauterized thoroughly. The wound was again closed with drainage. His condition remained essentially unchanged until the latter part of April 1939, when pneumonia developed. He died April 23. Autopsy revealed the immediate cause of death as bronchopneumonia. Sections through the

ulcerative area of the parietal region disclosed tongues of fairly well differentiated cells which seemed to be invading the tissue (fig. 11). The pathologic findings were considered to be fairly suggestive of squamous cell carcinoma.

*CASE 10.—Diploic dumbbell type of epidermoid in the right parietal region; operative removal and recovery.*

A 21 year old college student, while playing football on Nov. 27, 1937, was kicked on the right side of the head. He was not rendered unconscious. Toward night he began having severe headache accompanied by attacks of vomiting. The following day the headache continued to be very severe. Stiffness and soreness of the neck developed. He was taken to a hospital, where blood-tinged fluid was obtained on spinal puncture. He left the hospital December 1, feeling much better. Further questioning revealed that during the previous six months he had noticed a firm swelling in the right parietal region near the injured area.

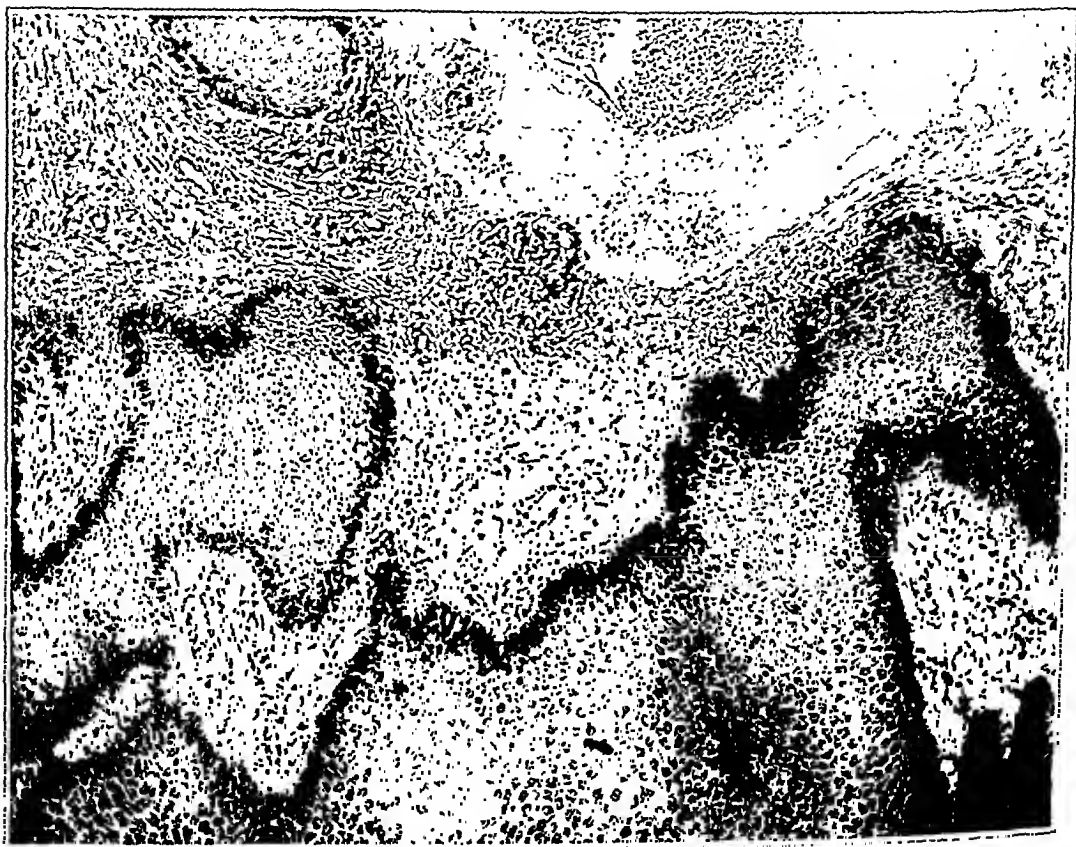


Fig. 11 (case 9).—Photomicrograph of the epidermoid, revealing extensive hyperkeratosis suggestive of squamous cell carcinoma.

*Examination.*—There was slight stiffness of the neck, and he complained of some headache and backache. In the right parietal region one could feel a depression in the skull admitting a finger tip. The surrounding scalp was not edematous and no hematoma was evident. Roentgenograms of the skull disclosed a round, somewhat irregular, lobular and in places a moth-eaten defect in the right parietal region (fig. 12). It was believed to be an epidermoid.

The patient was operated on December 8 and the incision exposed an area of eroded bone, from which protruded a pulsating bluish mass strongly resembling a hemangioma. It was opened cautiously, and about 1 fluidrachm (3.7 cc.) of old blood escaped. One could then see the typical structure of a dumbbell-shaped epidermoid. The skull was trephined, and a round button of bone which included the skull was removed, at which time the cholesteatomatous material could be seen escaping from the rent in the dura. A small round piece of dura including the rent was then removed. Cholesteatomatous material and old liquid blood came from the subcortical region, leaving a cavity 3 or 4 cm. deep. Around the edges

at the neck of the cavity some lining of the sac could be seen. These edges and the upper part of the wall of the cavity were thoroughly coagulated with the electrocautery. The only other alternative would have been resection of a rather large portion of the brain, which did not seem to be justifiable. Microscopic examination disclosed numerous flat, horny epithelial cells and numerous cholesterol crystals. A pathologic diagnosis of epidermoid was made.

*CASE 11.—Cranial dermoid posterior to the bregma near the longitudinal suture; operative removal and recovery.*

A 38 year old Italian laborer was referred on Jan. 23, 1939, for excision of a tumor of the scalp which was thought to be a sebaceous cyst. This had been present as long as he could remember but had become somewhat larger during the past year.

*Examination.*—A slightly fluctuant, nontender tumor mass about 3 cm. in diameter was evident to the left of the midline and posterior to the bregma. Roentgenograms of the skull disclosed a saucer-like depression of the outer table just posterior to the bregma and along the longitudinal suture. Preoperatively a dermoid cyst was diagnosed.

On February 2 the cystic tumor was carefully dissected from the depression in the outer table, after which closure was performed without drainage. Dr. Cyril B. Courville described the specimen as a cystic mass arising from a broad base which appeared to be a fibrous membrane. The tumor measured 3.6 by 2.8 cm. in diameter. Sections through the wall

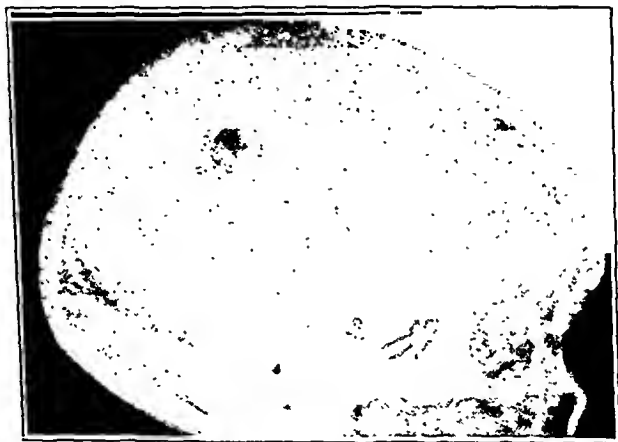


Fig. 12 (case 10).—Lateral roentgenogram of the skull, demonstrating a cranial epidermoid in the right parietal region.

revealed an epithelial lining of squamous to columnar cells with glandular structures in the underlying tissues. The diagnosis was dermoid cyst.

*Comment.*—That the diploic, or cranial, epidermoids may often be confusing unless one has their identifying roentgenographic characteristics in mind is evident from the 11 cases just presented. So typical is the roentgenographic appearance of the growths that usually the preoperative diagnosis can be established from the films. In spite of this fact these tumors are often undiagnosed. Four of the tumors in our series of cases were operated on as sebaceous cysts. In case 4 four operations were necessary before complete removal was effected. The diagnosis was established only after the roentgenograms of the skull were reviewed. After an incomplete removal of the cyst in case 5, the patient had repeated aspirations for a period of four years. She was then seen by some one familiar with the diagnosis. A review of the roentgenograms taken four years previously revealed the characteristic picture of a cranial epidermoid. Meningioma was thought the most likely diagnosis in case 7. Experience with this case, however, led to the proper diagnosis in case 3, which had not been appreciated when the patient was first seen, five years previously. Because the diploic, or cranial, epidermoids are so easily diagnosed

and can be treated so satisfactorily surgically, it is important that they be recognized before they reach a size which might make complete removal impossible. The importance of this fact is seen in case 9.

#### R. INTRACRANIAL EPIDERMIOIDS AND DERMIOIDS

*CASE 12.—Intracranial dermoid cyst in left temporal region; subtotal removal followed by complete extirpation a year later; cerebral abscess and death the following year; autopsy.*

This case was reported previously by one of us.<sup>28</sup> A woman of 40 years was operated on Nov. 11, 1922, at which time the contents of a dermoid were removed from the left-temporal region. Marked improvement followed the procedure and continued until recurrence of symptoms became manifest Feb. 1, 1923. Reexploration was carried out February 10, but an attempt to dissect the cyst from the floor of the skull was unsuccessful. Improvement again occurred until the middle of April, when reexploration was again necessary. On April 26 the cyst was emptied of its contents and the entire cyst wall removed. The patient again improved until the following September, when it was necessary to reexplore. At this time no trace of the cyst was found, but a mass about 4 cm. in diameter, which proved to be an abscess, was removed from the left temporal lobe. Cultures were sterile. The patient's condition remained critical. The right hemiplegia and motor aphasia persisted until her death, on March 17, 1924. Pathologic examination of the dermoid cyst showed that its wall resembled true dermis, containing hair follicles, sweat glands and stratified squamous epithelium. The central mass was filled with debris composed of desquamated cells, among which were scattered fine hairs and cholesterol crystals.

*CASE 13.—Parapituitary epidermoid disclosed at operation; partial removal.*

A boy 9 years old was admitted to the hospital June 20, 1928. This case was tabulated as one of postchiasmal cholesteatoma in the third ventricle in a report on tumors of the brain in childhood published by Rand and Van Wagenen<sup>29</sup> in 1935. According to the history the patient had complained of frontal headaches unassociated with nausea or vomiting during the previous five years. His appetite became poor in January 1928, and he lost weight and tended to be listless. Although his eyes were noticeably prominent, his parents were uncertain how long this had been apparent. During the previous year they believed his disposition had changed. He was disobedient, quarreled with other children and seemed to prefer being alone.

*Examination.*—The patient was a poorly nourished boy of 9 years, who seemed mentally retarded. The fundi showed no indication of pressure. The pupils were equal and reacted well and equally to light and in accommodation. The eyes were prominent. A tendency to internal strabismus, left more than right, was noted. A horizontal nystagmus was present on gaze right and left, and vertical on looking upward. There was a slight left peripheral facial weakness. Hearing was markedly impaired in the left ear, and in the Weber test the sound was referred to the right. Otherwise the cranial nerves disclosed no peculiarities. Coordination tests revealed more or less equal ataxia of the extremities, more noticeable in the legs than in the arms. The Romberg sign was present, the patient swaying in all directions. His gait was ataxic. He staggered in all directions, but somewhat more to the right than in other directions. Deep reflexes were equal and active. Nothing unusual was discovered in the remainder of the neurologic examination. Vestibular examination suggested a lesion of the left cerebellopontile angle or a cerebellar lesion extending into the left angle.

It was believed the patient had a lesion of the posterior fossa, and exploration was advised. He was, however, taken to the Mayo Clinic where Dr. A. W. Adson reported that calcification above the sella turcica was seen roentgenographically. A bitemporal hemianopsia was also discovered, leading to the diagnosis of a supratentorial cyst in the neighborhood of the chiasm. At operation on July 31, 1928, a slightly cystic tumor was discovered, arising in the region of the sella turcica and extending posteriorly into the third ventricle. A portion of the tumor presenting anteriorly to the chiasm was removed and the cyst aspirated, after which an intracapsular enucleation of the lesion was accomplished. The patient made an uneventful recovery.

28. Rand, C. W.: Intracranial Dermoid Cysts: Report of a Case, with Operative Findings, *Arch. Neurol. & Psychiat.* 14:346 (Sept.) 1925.

29. Rand, C. W., and Van Wagenen, R. J.: Brain Tumors in Childhood, *J. Pediat.* 6:322, 1935.

Pathologic examination of the tumor tissue disclosed a "calcareocholesteatoma" with a large amount of blood pigment and numerous foreign body giant cells surrounding cholesterol crystals.

*Comment.*—The case is of interest from the standpoint of diagnosis. Had we appreciated the calcification revealed by the roentgenogram and discovered the bitemporal hemianopsia, the localization would have been established. The importance of appreciating that such chiasmal neoplasms may simulate the signs and symptoms of the more common cerebellar tumors of childhood becomes evident.

*CASE 14.—Epidermoid of the left cerebellopontile angle disclosed at operation and removed subtotally; death four years later.*

A married woman, aged 56, was admitted to the hospital July 8, 1929. During the previous five years she had been troubled with pain in the left side of her head, ringing and deafness in the left ear and numbness and weakness of the left side of the body. During the last two years she had had spells of staggering and falling while walking. The past year she had occasionally regurgitated food through her nose. Diplopia had been present for about three months.

*Examination.*—Except for obesity the general physical examination revealed nothing noteworthy. The disks were not choked. There was, however, a weakness of the left external rectus muscle, with horizontal nystagmus more marked on gazing to the right than to the left, corneal anesthesia on the left, with diminished pain and touch sensation over the distribution of the left trigeminal nerve, and a slight left lower facial weakness. Hearing was impaired in the left ear with bone conduction greater than air conduction. The pharyngeal reflex was absent, with the uvula pulling to the right. She also had some dysphagia, a slight weakness of the left arm and leg and a slight impairment of sensation over the left side of the body. The Babinski reflex was positive on the left and equivocal on the right. The Wassermann reaction of both the blood and the spinal fluid was negative. Roentgenograms of the skull taken July 10 revealed nothing abnormal. Roentgenograms of the mastoid taken July 12 showed a normal internal auditory meatus with no indication of erosion in the Towne position. The impression was that of a tumor of the cerebellopontile angle on the left side, and exploration was advised. Vestibular tests performed August 10 showed no response from either the horizontal or the vertical canals on the left side and no response from the vertical canals on the right. At this time her gait was markedly ataxic, affecting the left side almost exclusively.

A suboccipital exploration was carried out August 15. Because her condition became rather critical at this time, it was decided to postpone further operation. When the left cerebellar angle was explored, on October 3, a pearly, glistening, irregular-shaped tumor was found. A large amount of cholesteatomatous tissue was removed by subcapsular enucleation. It was not possible to remove the capsule entirely. On June 9, 1930, her condition was reportedly unimproved. She died on Nov. 1, 1933, but autopsy was not permitted.

The surgical specimen was composed of numerous bits of gray, glistening material. Portions of the capsule particularly had a mother-of-pearl luster and were finely nodular. Microscopic examination confirmed the diagnosis of epidermoid.

*CASE 15.—Dermoid cyst between the cerebellar lobes accidentally found at autopsy in a woman of 60 years.*

This woman had been admitted to the hospital several times for bronchitis and for fractures of various bones, the case being reported previously by Courville.<sup>27</sup> She came somewhat irregularly to the hospital for antisyphilitic therapy from 1930 to 1935, and died at home Jan. 13, 1936. Her body was brought to the hospital for examination at the coroner's request.

Dr. Courville, who examined the brain, described a peculiar orange appearance and a granular body in the vallecule of the cerebellum. When the arachnoid was torn this structure appeared as a granular, yellowish body lying beneath the inferior vermis. The tumor mass was friable and granular on section and contained some calcium. The tumor itself appeared to be formed by a cyst, the contents of which were lipid, containing considerable cholesterol and a few hairs. Microscopically the wall was seen to be composed of dense fibrous epithelium or tissue lined with a layer of stratified squamous epithelium. A number of small calcareous deposits or particles were seen throughout the walls. The wall was intimately attached to the folia in this region. Because of the presence of hair it was felt to be a dermoid rather than an epidermoid cyst.



CASE 16.—*Left-sided convulsions for eighteen years; coma and death following a seizure; autopsy; epidermoid of the right parietal region; acute cerebrospinal (epidemic) meningitis.*

A 58 year old man was admitted to the hospital in coma on Dec. 12, 1932. Left-sided jacksonian attacks had occurred at monthly intervals since 1914. After a severe attack in 1921 he lost control of the lower extremities, bladder and bowels, fair control being restored by the end of a six month period. Two weeks prior to his admission to the hospital he had a mild attack of influenza, and on the night of December 9 a convulsion occurred. The following day he improved, but on the evening of December 11 he became worse, and on December 12 he lapsed into coma.

The past history revealed a gastroenterostomy in 1921 for duodenal obstruction. Shortly after the onset of his convulsive seizures the diagnosis of tumor of the brain was made, but nothing further was done in this regard. He complained occasionally of headache. The past history otherwise revealed nothing of consequence.

*Examination.*—A complete neurologic examination was not recorded, but it was noted that the pupils were circular and equal and reacted equally to light. The deep reflexes were equal but sluggish, and the Babinski reflex was positive bilaterally. The blood pressure was



Fig. 13 (case 16).—Photograph of coronal sections of the brain, showing an intracranial epidermoid in the parietal lobe of the right cerebral hemisphere.

150 systolic and 100 diastolic. Urinalysis showed large quantities of albumin, numerous granular casts, occasional hyaline casts and many erythrocytes. The nonprotein nitrogen was 64.5 mg. per hundred cubic centimeters. The erythrocyte count was 4,300,000 and the leukocyte count 17,000.

Autopsy was performed by Dr. J. W. Budd. Gross examination of the brain revealed a thick purulent exudate over the lateral surface of the hemispheres. When the brain was removed a considerable quantity of cloudy fluid escaped from the posterior fossa. The base was covered by a thick purulent exudate which obscured the various vessels and nerves. When the serial coronal sections were made an indurated area 2 by 1 cm. was discovered in the parietal lobe of the right cerebral hemisphere. This subcortical tumor was about 1.5 cm. lateral to the median line. The defect was filled with a yellowish green, gritty material, somewhat inspissated and friable, with tiny glistening spots on the sectioned surface (fig. 13). A smear of the material disclosed many cholesterol crystals. Microscopic examination revealed a cyst wall, the outer part of which was made up of dense glial scar tissue, while the inner part was dense, fibrous scar tissue. This fibrous lining was apparently continuous with the fibrous tissue of the pia at the depth of a sulcus. The cyst contained a granular, structureless form of debris showing many lenticular clefts (cholesterol crystals) and foci of calcification. An epithelial lining was not evident in the microscopic sections. The adjacent cerebral tissue

showed distortion from pressure, with increase of the glial supporting tissue and atrophy of the parenchyma. There was an extensive inflammatory process of the meninges, with exudate consisting largely of polymorphonuclears. When the dura was reflected from the spinal cord, it was found to be covered by a thick veil of yellowish, opaque exudate. Although micro-organisms were not seen in the tissue sections, direct smears stained with Gram stain showed intracellular gram-negative diplococci. It was not possible to obtain the organism in culture. Dr. Budd concluded on the basis of the smear findings that acute cerebrospinal epidemic meningitis was the terminal event. There was in addition an epidermoid involving the cortex of the parietal lobe along the right median surface. Additional findings of interest included two diverticula of the intestinal tract and a gastroenterostomy with a small marginal ulcer.

*CASE 17.—Increasing right hemiparesis for five years; roentgenograms revealed a group of calcifications measuring 2 inches (5 cm.) in all dimensions lying within the left middle fossa of the skull; operative removal of a large subdural epidermoid; death and autopsy.*

A married man aged 39, a truck driver, was referred on July 16, 1935. His first symptoms occurred in 1929, with pain in the right forearm radiating down to the hand and up to the shoulder. Later pain was noticed in the right leg. Difficulty in using the right hand, which was observed in 1930, continued and increased. Dragging of the right foot appeared in 1931 and continued thereafter. Increasing numbness of the right side developed. During the past year difficulties in speech occurred, in that sometimes he was unable to talk, although he knew what he wanted to say. There was also difficulty in reading and in writing. During the previous year, and especially during the last three or four months, he had suffered severely with headaches, the pain being mainly in the right occipital region. Since 1930 the patient had had occasional jacksonian seizures involving the right side of the body. Occasionally he was troubled with nausea and vomiting. He had noticed no impairment of vision or hearing, and prior to his present illness his general health had been good.

*Examination.*—This patient was obviously handicapped by right hemiparesis and by difficulty in speech. Funduscopic examination showed somewhat hazy disk margins with overfilling of the veins, but no measurable elevation. There was a noticeable weakness of the right side of the face, central in character. The visual fields showed no constriction on rough testing. There was a complete astereognosis of the right hand, a right hemiparesis amounting to a complete paralysis of that hand and pronounced weakness of the right side of the face as well as less weakness of the right leg. The Romberg sign was present, the gait being so hemiplegic that the man was barely able to walk. The abdominal and epigastric reflexes were sluggish on the right and active on the left. All of the deep reflexes were hyperactive on the right and active on the left side. Ankle clonus was present on the right and absent on the left. The Babinski reflex and allied signs were positive on the right and negative on the left. The blood pressure was 150 systolic and 90 diastolic.

Roentgenograms of the skull demonstrated a large group of small calcifications, measuring approximately 5 cm. in all three dimensions, lying within the left middle fossa of the skull. The lower margin of this area was about 1 cm. above the level of the clinoid processes.

At operation Aug. 8, 1934, a firm nodular tumor could be felt directly under the dura in the left temporal region. Opening of the dura disclosed a large epidermoid which measured about 8 by 6 by 4 cm. in various diameters. It resembled a potato with nubbins on it. Its contents consisted of a cheesy material which was often pearly white. The tumor had a definite capsule which was thin and had many ramifications. During closure of the wound the patient suddenly died. At autopsy Dr. Cyril B. Courville reported the essential pathologic changes to be in the region of the left sylvian fissure, where two large irregular openings in the membrane were noted, the posterior one measuring 4 by 4.7 cm. in diameter. Beneath the thickened and opaque leptomeninges in the sylvian fissure, the remnants of an epidermoid were observed. Nodules of this tumor were found in the superior surface of the left temporal lobe, while down in the depths of the cavity the tumor was evident in irregular masses. At its greatest depth the cavity actually measured 6 cm. The gross diagnosis was epidermoid (pearly tumor) of the left sylvian region, with operative subtotal removal.

A section was taken from the nodule of the epidermoid still present in the brain. The line between the tumor and the brain was not very distinct, since the superficial cells of the tumor lay in such intimate relationship with the brain substance. These cells, however, were quite characteristic.

*CASE 18.—Large epidermoid in the left cerebellar region; incomplete operative removal; death six days later.*

A 57 year old engineer was examined on Aug. 31, 1936 by Dr. Cyril B. Courville and, in consultation with one of us, on September 2 of the same year. Some twenty years previously the patient had first been troubled with tinnitus in the left ear, which persisted for about seven

years before disappearing. With the onset of the tinnitus his hearing became impaired, and by the time the tinnitus had ceased the left ear was deaf. About 1926 he experienced periodic pain in the occipital region, which he described best as a sense of pressure. With the pressure symptoms he often saw double. In a few months this disappeared, but it returned again during the last few years. About 1927 he noticed short spells of unsteadiness lasting only a few seconds at a time. Two years later they disappeared, and instead there developed a gradually progressive feeling of unsteadiness, particularly in the left hand and leg. In 1932 or 1933 the patient discovered a weakness of the left side of the face which became gradually more pronounced.

*Examination.*—The fundi were normal. A pronounced weakness of the left external rectus muscle was evident, and the patient saw double when looking straight ahead or to the left. There was a noticeable horizontal nystagmus on looking either to the right or to the left, of wider amplitude on looking to the left but more rapid on looking to the right. The corneal reflex was diminished on the left, and the same was found to be true of sensation over the left trigeminal area. The motor division of the fifth nerve was intact. There was a moderate peripheral weakness of the left side of the face. The ticking of a watch was heard at a distance of 2 feet (60 cm.) from the right ear, but was not heard when the watch was pressed against the left ear. Air conduction was better than bone conduction on the right, but bone conduction was better than air conduction on the left. In the Weber test the sound was not lateralized. The cranial nerves were otherwise intact. Tests for coordination disclosed noticeable ataxia of the left arm and leg. The Romberg sign was present, the patient swaying backward and to the right. He tended to walk on a wide base and was slightly ataxic. Anteroposterior roentgenograms of the skull revealed an erosion of the left porus acusticus internus. It was believed the patient had an acoustic neuroma on the left side.

He was subsequently operated on, November 3, by Dr. H. C. Naffziger, who was surprised to encounter a pearly tumor when he elevated the left cerebellar lobe. He curetted out a large amount of characteristic flaky, white material. The sac had eroded through the bone about midway between the foramen magnum and the tip of the petrous bone. The cyst extended in front of the medulla and then around into the cerebellum and into the left cerebellar tonsil. All possible material was curetted out, and the accessible portions of the capsule were removed. The patient's postoperative condition became critical, and he died six days later.

Dr. Courville reported that the histologic sections presented a classic parallel fibrous structure arrangement, staining feebly. A condensed distended portion, which apparently was the capsule of the growth, stained a bluish pink. The remaining portion of the tissues showed the classic wood fiber arrangement usually found in these pearly tumors.

*CASE 19.*—*Epidermoid of the right cerebellopontile angle partially removed Dec. 16, 1936; reexploration and complete removal of the tumor Feb. 10, 1937; recovery.*

A married woman of 19 years entered the hospital Dec. 17, 1936, complaining of headaches for two years, progressive unsteadiness of gait for six months, and blurred, failing vision for four months. In 1935 the intensity and frequency of the headaches increased, and they were frequently accompanied by vomiting. During September 1936 her vision began to fail, and by October she was unable to read print. Disturbance of equilibrium was first discovered during July 1936. Gradually she began to stagger more to the right than to the left. This progressed slowly, so that at the time of her admission she could not walk unassisted.

*Examination.*—The patient was unable to recognize the usual test odors in each nostril. Funduscopic examination revealed bilateral papilledema of 1 to 2 diopters. Her pupils were somewhat dilated and irregular, reacting sluggishly both to light and in accommodation. Nystagmus was noted in all directions, but otherwise the extraocular movements were normal. The corneal reflexes were bilaterally sluggish. Perception of the ticking of a watch seemed diminished in each ear, and perception of sound from a tuning fork was lateralized to the left ear. The remaining tests of cranial nerves gave normal results.

Although well oriented, she was somewhat lethargic and at times facetious. Rough testing of the visual fields suggested concentric constriction. Coordination tests of the upper and lower extremities demonstrated some ataxia bilaterally. The Romberg sign was present. Her gait was ataxic; she fell toward either side. The superficial and deep reflexes were equal and active, the Babinski reflex and allied signs being negative. The blood pressure was 115 systolic and 85 diastolic. Laboratory examinations, including urinalysis and blood count, gave normal results, and the Wassermann reaction of the blood was negative. Roentgenograms of the skull taken Dec. 10, 1936 revealed a slight separation of the sutures. There was also a beaten silver appearance of the skull, and the dorsum sellae showed some erosion.

A suboccipital craniotomy was performed December 16 by Dr. R. B. Raney. A solid tumor was palpable under the dura over the vermis. When the dura was opened a pearly mass was

exposed, overlying the medulla and the vermis. The surrounding capsule was so densely adherent that removal was impossible. It was therefore opened and the white caseous material removed, after which the wall was electrically cauterized and closure carried out in the usual manner.

Dr. Cyril B. Courville reported on a mass of irregular fragments of grayish or pearly white tumor tissue taken from the midline of the cerebellum. The fragments of capsule showed the typical mother-of-pearl appearance. The histologic sections revealed only a small amount of shredded linear material staining pink, which was characteristic of an epidermoid.

The patient returned to the hospital Feb. 5, 1937, unimproved. She was reoperated on February 10, by Dr. Raney, and the remaining capsule, which had been destroyed by cautery during the first procedure, was completely removed. After the second operation she gradually improved. When she was examined Dec. 9, 1938 her vision was steadily improving.

*CASE 20.—Basilar epidermoid in the left frontal region accidentally found at autopsy.*

A white man of 68, a WPA worker, first entered the hospital Feb. 14, 1937, in the medical service, with the history of passing tarry stools two or three days previously. The morning before his admission he fainted and was unconscious for an indefinite period of time. After this he had three episodes of vomiting and lost about a pint of blood. Fluoroscopic examination March 4 revealed an ulcer at the base of the duodenal bulb. Two more or less similar episodes with admission to the hospital occurred March 24, 1937 and May 2, 1939. On the last occasion, however, severe hemorrhage again occurred, which resulted in his death. After autopsy the cause of death was reported as atrophic cirrhosis of the liver, with esophageal varices and massive hemorrhage.

Postmortem examination of the brain revealed a sharply outlined, encapsulated pearly tumor, measuring 2.1 cm. transversely and 2.5 cm. anteroposteriorly, which was embedded in the middle and posterior portions of the basilar surface of the left frontal lobe. Microscopic examination showed it to be an anuclear structure made up of strands and layers of fibrous material. In the examined section none of its peripheral membranes were present, but the study of the section itself strongly suggested the diagnosis of an epidermoid.

*CASE 21.—Epidermoid of the left cerebellopontile angle; death after operation; autopsy.*

A laborer of 41 entered the hospital June 11, 1937, complaining of failing vision since 1932, pain in the back of the head since 1933 and dizzy spells, tremor of the left leg and weakness of the left hand for the past four months. Since 1931 he had been bothered with periods of depression. He volunteered the information that he thought there was "something loose" or a tumor in his head. For some ten years he had noticed increasing impairment of hearing in the left ear, and for four years there had been ringing in that ear.

Examination showed blurring of both optic disks, with numerous hemorrhages in both fundi. Horizontal nystagmus occurred on gaze right and left, and rotary nystagmus on upward gaze. The pupils were circular, equal, and reacted well and equally to light and in accommodation. Marked hypesthesia was noted over the three divisions of the right trigeminal nerve, with absence of the corneal reflex on that side. There was also a weakness of the lower part of the face. By gross testing some impairment of hearing was discovered in the left ear. Speech seemed somewhat thick. Rough testing revealed that the visual fields were contracted moderately. Tests for coordination revealed some ataxia of the upper extremities, particularly the left, but no significant incoordination of the lower extremities. The Romberg sign was absent, and the gait was normal except for a tendency to fall with rapid turning.

Roentgenograms of the skull, including the Towne position, demonstrated no pathologic conditions and showed no evidence of increased pressure. Vestibular tests indicated some impairment of the responses on the left side, and hearing tests revealed some impairment for the higher frequencies. A lumbar puncture yielded spinal fluid with an initial pressure of 350 mm., clear and colorless, with a normal cell count and a negative Wassermann reaction. The Wassermann reaction of the blood was also negative.

Preoperatively it was thought that the patient had a left-sided cerebellar tumor. A suboccipital craniotomy was performed June 23, 1937 by Dr. G. H. Patterson. After the dura was opened and the lateral surface of the left cerebellar lobe removed, a large epidermoid was exposed. It extended into the angle, compromising the seventh, eighth, ninth, tenth and eleventh cranial nerves. By means of a curet and cautery almost all of its contents and capsule were removed. The entire mass seemed the size of a tangerine. The patient's condition was poor. He failed to improve, and in spite of the usual supportive therapy he died that night. An autopsy was performed, and the brain was examined by Dr. C. B. Courville. The specimen consisted of numerous fragments with a nodular surface and mother-of-pearl appearance. Study of a section through one of the fragments showed a narrow remnant of

surface epithelium, forming a dark purple border of the cell. The tissue beneath occurred in the form of a loose parallel arrangement of the strands of structureless material characteristic of the tumor. The microscopic diagnosis confirmed the gross impression of epidermoid.

*CASE 22.—Parapontile epidermoid accidentally found at autopsy.*

A 54 year old woman was admitted to the medical service June 21, 1937. About three weeks previously she had become intoxicated, and as a result she was kept in custody for about five days. Because her condition failed to improve she was transferred to the hospital for diagnosis and treatment. She had had frequent spells of dyspnea and coughing with expectoration of blood-streaked sputum. Roentgenograms of the chest showed abnormal hazy density of almost the entire left pulmonary field, indicating a long-standing intrapulmonary tuberculosis. The Wassermann and the Kahn reaction of the blood obtained June 23, 1937 were negative. Because of the advanced pulmonary tuberculosis the patient was referred to the nearest county tuberculosis clinic.

She was again seen Dec. 29, 1937, when she was brought into the hospital in coma, with the diagnosis of a cerebral accident and a right-sided hemiplegia. Death occurred the following day, and an autopsy was performed by the coroner. His observations included a small extradural hemorrhage and a large subdural hemorrhage over the left frontal lobe of the brain. There was also evidence of old tuberculosis with cavitation in the left upper pulmonary lobe.

In the brain Dr. Cyril B. Conville found moderate thickening of the leptomeninges on the dorsolateral surfaces of the frontal lobes, and the remains of a subdural hemorrhage over the dorsolateral surface of the left cerebral hemisphere. A typical pearly tumor was found, spreading over the base of the pons and medulla and extending into the cerebellopontile angle on each side. The appearance of the tumor was characteristic; it had a brilliant pearly surface and the capsule disclosed a whitish material beneath. Microscopic examination corroborated the gross diagnosis of epidermoid.

*CASE 23.—Parapituitary epidermoid; partial removal and operative recovery.*

A 16 year old high school girl was referred on April 28, 1938. She had noticed loss of vision in the right eye since 1931, and progressive loss of vision in the left eye since March 1938. In 1934 only a slight acuity remained in the right eye. The first intimation of impairment of vision of the left eye occurred during March of 1938, when she discovered she was unable to see as clearly as before. By April 1 she had difficulty in reading, and from that time she felt there had been a slowly progressive impairment of vision. Although the patient was unable to state exactly when her headaches began, she believed they were related to the failure of vision. At first the headache was present every week and seemed to involve mainly the region of the right eye. She recalled that about three years before she had suffered almost daily with headaches over this area. Usually they occurred in the afternoon and lasted a few hours. During the past two years these headaches occurred about twice a week and would last a good part of the day. After the failure of vision in the left eye, she also had some pain in this eye. Occasionally in the last two years she had been somewhat dizzy on getting up in the morning.

The fundi showed an atrophic bluish white disk on the right side. The atrophy of the left disk was more marked on the temporal than on the nasal side. The right eye was blind. With correction the vision in the left eye was 5/15. The cranial nerves were otherwise found to be intact. The left visual field showed a temporal hemianopsia. The rest of the neurologic examination disclosed nothing noteworthy. Roentgenograms of the skull taken April 13 revealed convolutional bony atrophy, suggesting increase in intracranial pressure. The sella turcica was normal. The Wassermann reaction of the blood was negative. The spinal fluid was under an initial pressure of 190 mm. and was clear and colorless; there was no globulin, and the Wassermann reaction was negative.

Ventriculography on May 4 showed nothing significant. In view of the failing vision and the left temporal hemianopsia, a pituitary exploration was performed. Exposure of the sellar region uncovered a glistening mass, the contents of which were the flaky material typical of cholesteatoma. A large amount of this material was removed along with some of the membrane of the cyst. The actual extent of the tumor could not be determined, but it was believed complete removal was impossible.

Dr. R. W. Hammack reported that the specimen consisted of a large amount of gray or pale yellow material. In places the surface was distinctly pearly. Microscopic examination revealed innumerable squamous epithelial cells and a few cholesterol crystals. The diagnosis was epidermoid cyst. Although the patient has remained well symptomatically, there has been no improvement in her vision. Both optic nerves were bluish white. The visual fields made at this time were essentially the same as those previously taken.

*Comment.*—In contrast to the diploic or cranial epidermoids, the results with the intracranial epidermoids are far less satisfactory. This is due to the fact that they are less accessible and their capsules may be so intimately associated with vital structures that complete removal is impossible. The 4 cases of epidermoids of the cerebellopontile angle reveal symptoms and signs similar to those of acoustic neurinomas. The epidermoids, however, show a greater involvement of the adjacent cranial nerves than is usual with acoustic neurinomas.

#### PATHOLOGY

From the time of von Remak's<sup>30</sup> excellent publication in 1854, in which he expressed his opinion that these rare neoplasms resulted from epithelial rests, numerous views have been advanced concerning them. For the most part they have merely corroborated his original conception. Virchow<sup>31</sup> considered all of them due to disturbances of development, and was supported by Mikulicz<sup>31</sup> in 1879 and by Kuster<sup>32</sup> in 1889. He classified them as heterologous tumors arising in the connective tissue. Though it seems evident he regarded them as epithelial, he confused his contemporaries by comparing them with canceroids.

Perls,<sup>33</sup> the first to challenge von Remak's epithelial hypothesis, was of the opinion that these tumors came from the endothelium of the neural lymph spaces; others, including Klebs<sup>34</sup> in 1889, Schmaus<sup>35</sup> in 1895 and Glaeser<sup>36</sup> in 1890, agreed with him. This is more easily appreciated when it is realized that after Müller<sup>32</sup> had devised the term, a variety of tumors came to be called "cholesteatoma" with little regard to their cellular origin, for no other reason than that they contained cholesterol crystals. The interpretation of these tumors became further complicated by the occasional tendency of endothelial growths to copy the structure of cholesteatoma. Such an example is the so-called cholesteatoma of the choroid plexus which Klebs<sup>34</sup> correctly believed to be endothelial in origin. These intraventricular tumors are not comparable to the usual cholesteatoma, and Blumer's<sup>37</sup> term of "cholesteatomatous endotheliomata" is probably quite suitable. Certain of the suprasellar cysts of pharyngeal (Rathke's pouch) origin have similarly complicated the nomenclature. Cholesterol crystals are precipitated in the fluid contents of some of these cysts, and although they undoubtedly originate from epithelial rests dating from an early period of development, these inclusions are of pharyngeal rather than of cutaneous origin and have fluid contents in place of the fatty mass of desquamated cells or cholesteatoma proper.

Critchley and Ferguson<sup>6</sup> felt that in spite of the endothelial theory of Klebs, Perls, Nehr Korn and Kakeshita, they could subscribe only to an epithelial hypothesis for the origin of these tumors. It seemed to them that the most obvious probability was that more than one type of tumor had been described as "cholesteatoma," the

30. von Remak, R.: Ein Beitrag zur Entwicklungsgeschichte der krebshaften Geschwülste, *Deutsches Arch. f. klin. Med.* 6:170, 1854.

31. Mikulicz, cited by Kay, F. A., and Pack, G. T.: Cholesteatoma of the Brain: Report of a Tumor of Unusual Size, *Arch. Neurol. & Psychiat.* 19:446 (March) 1928.

32. Kuster, cited by Kay, F. A., and Pack, G. T.: Cholesteatoma of the Brain: Report of a Tumor of Unusual Size, *Arch. Neurol. & Psychiat.* 19:446 (March) 1928.

33. Perls, M.: *Lehrbuch der allgemeinen Pathologie für Studierende und Aerzte*, Stuttgart, F. Enke, 1877, vol. 1, p. 486.

34. Klebs, G.: *Die allgemeine Pathologie*, Jena, Gustav Fischer, 1889, vol. 2, p. 627.

35. Schmaus, H.: *Grundriss der pathologischen Anatomie*, ed. 9, Wiesbaden, J. F. Bergmann, 1910, p. 241.

36. Glaeser, E.: Untersuchungen über Cholesteatome und ihre Ergebnisse für die Lehre von der Entstehung der Geschwülste, *Virchows Arch. f. path. Anat.* 122:389, 1890.

37. Blumer, G.: Bilateral Cholesteatomatous Endotheliomata of the Choroid Plexus, *Johns Hopkins Hosp. Rep.* 9:279, 1900.

usual variety being clearly epithelial. The other group which Klebs,<sup>38</sup> Kakeshita<sup>39</sup> and others<sup>40</sup> have described was without doubt endothelial.

Martin, Dechaume and Puig<sup>39</sup> pointed out that the two main possibilities of origin of the epidermoids were that they developed either from a fetal inclusion of epithelial cells or as a result of metaplasia of the endothelial cells of the meninges. Virchow, Eberth and later Glaeser favored the idea of metaplasia. As pointed out by Critchley and Ferguson,<sup>40</sup> however, if the metaplasia theory were correct, one would expect to find transition forms between the epithelial and the endothelial elements in the same tumor, something they were unable to demonstrate. In agreement with most others, they expressed the opinion that these neoplasms occurred as a result of a fetal inclusion of epidermal cells, which, depending on the depths of the layer or according to the embryonic age, produced either an epidermoid or a dermoid type of tumor.

Closure of the medullary groove occurs at the beginning of the third week of fetal life, when constrictions appear in the formation of the three primary cerebral vesicles. Most writers accept Bostroem's conception that misplaced cells from the dermal or epidermal anlage give rise to the dermoid or epidermoid tumors found in the midline of the brain. During the fourth and fifth week, when the secondary vesicles are developing in the forebrain and the metencephalon and the myelencephalon are becoming differentiated in the hindbrain, cell rests that are misplaced may lie away from the midline.

Such hypothesis affords a reasonable and adequate explanation for the occurrence of the majority of epidermoids: those, in other words, arising from the basal excavation of the brain. It does not, however, account for the origin of the intracerebral tumors and the intradiploic and the cholesteatomatous growths within the spinal canal. However, there seems no reason why the same factor of cell inclusion is not similarly tenable. Critchley and Ferguson<sup>40</sup> pointed out, moreover, that the explanation of the occurrence of epithelial elements in association with the membranes become intelligible. This is based on the investigations of Harvey and Burr<sup>40</sup> on meningeal development, in which they demonstrated that certain ectodermal elements, derived in large part from the neural crest, are contributed to the mesenchyme and take part in the formation of the leptomeninges.

The cholesteatomatous masses associated with chronic suppurative conditions of the middle ear have generally been considered entirely different lesions. They result from a chronic inflammatory desquamative process and are not neoplastic as are the true dermoids. In contradistinction to the primary or true tumor, this secondary type of cholesteatoma has also been called caseous metamorphosis, inflammatory cholesteatoma and cholesteatosis.

Wingrave<sup>41</sup> expressed the belief that the cholesteatomatous formation in the ear occurred after prolonged persistence of perforations of the tympanic membrane, as a result of the replacement of the normal epithelium of the middle ear by squamous epithelium. It was his opinion that this metaplasia involved not only the tympanum but the adjacent pneumatic spaces as well and that the rapidly growing new epithelium accumulated because cytotoxicity and disposal were difficult. Variations of this theory have been expressed by numerous otologists.

38. Kakeshita, T.: *Zur Pathologie der Hirn-Cholesteatome*, Arb. a. d. neurol. Inst. a. d. Wien. Univ. 27:327, 1925.

39. Martin, J. F.; Dechaume, J., and Puig, R.: *Morphologie et histogénèse des tumeurs méningées crâniennes*, Ann. d'anat. path. 5:277, 1928.

40. Harvey, S. C., and Burr, H. S.: *Development of the Meninges*, Arch. Neurol. & Psychiat. 15:545 (May) 1926.

41. Wingrave, V. H. W.: *Notes on the Pathogeny of Cholesteatomata*, J. Laryng. 25:339, 1910.

Those favoring metaplasia of the mucous membrane of the middle ear as the explanation of this problem have not been without criticism. One of the main difficulties has been to account for the manner in which a tumor composed of stratified and horny epithelial cell elements might arise in a cavity lined with columnar epithelium. It has also been pointed out that mere epidermal invasion of the middle ear is not sufficient to cause cholesteatomatous growth. As early as 1878 Schwartz<sup>42</sup> described epidermic blind pouches jutting into the middle ear and persisting throughout life without tumor formation. Rare cases, moreover, have been reported in which no perforation of the ear drum was demonstrable through which epidermal invasion could take place. It was probably for this reason that the theory of metaplasia of the antrotympanic membrane arose. Such a cholesteatoma usually follows marginal rather than central perforations of the eardrum. Wingrave<sup>43</sup> has compared the mechanism with the well recognized phenomenon in which rectal and nasal polyps undergo transformation of their surface into a stratified or horny type of tissue when they protrude permanently from their orifices.

Another type of cholesteatoma rather infrequently encountered by otologists is that variety originating within the mastoid air cells, one which apparently develops without the necessity of either tympanic perforation or sepsis. Lucae<sup>42</sup> in 1873 was one of the first to record a cholesteatoma arising in the mucous membrane of the tympanic cavity with no evidence of perforation of the eardrum nor any indication of aural disease.

Cushing<sup>44</sup> was of the impression that many of the cholesteatomas reported by otologists were true epidermoid tumors, originating from aberrant epidermal rests laid down in the temporal bone during the early formation of the complicated special sense organ it contains. He expressed the opinion, moreover, that it was not improbable in many of the recorded cases that the cholesteatoma itself was responsible for the otitis media, rather than the reverse. The possibility that the cholesteatomas of the petros and of the mastoid are merely examples of the larger class of diploic or cranial epidermoids merits further consideration and investigation.

Ordinarily the gross appearance of an epidermoid is so characteristic that a correct pathologic diagnosis can be rendered at sight. So striking is the glistening white capsule that it has seldom failed to impress the observer. Often the contents of the epidermoid tend to fragmentation, although caseation and necrotic change may occur in tumors of long standing. The dermoids, on the other hand, are often soft with cystic consistency. Although they frequently have a pearly sheen, their color is more likely to be an opaque yellow. The presence of sebaceous material, fat and cholesterol crystals in varying proportions determines the consistency of the dermoids, and usually they contain hairs, coiled, clumped or matted together. It has been considered that the presence of hair may be regarded as pathognomonic of the dermoid or teratoid type of growth. On cross section an epidermoid has a uniform consistency and contains a finely granular, white or creamy yellow material which tends to be laminated. If the section is made in another plane, it has a concentric laminated appearance not unlike that of an onion. The surface of the tumor, moreover, has a soapy or waxy quality. The absence of vascularity is a noteworthy feature of the epidermoids. In most cases a definite point of attachment and a more or less intimate association with the pia-arachnoid are demonstrable.

42. Schwartz, H.: *Pathologische Anatomie des Ohres*, Berlin, A. Hirschwald, 1878.

43. Lucae, J. C. A. L.: *Arch. f. Ohrenh.* 1:225, 1873.

44. Cushing, H.: A Large Epidermal Cholesteatoma of the Parietotemporal Region Deforming the Left Hemisphere Without Cerebral Symptoms, *Surg., Gynec. & Obst.* 34:557, 1922.



Histologically there is a close resemblance between the dermoids and the epidermoids, but, as the name implies, the epidermoids consist only of ectodermal derivatives, while the dermoids are characterized by ectodermal epidermis plus mesodermal corium with its connective tissue, fat cells, sebaceous glands and hair follicles. The dermoids consist of a fibrous outer layer, a connective tissue stroma and an epithelial inner layer. The connective tissue matrix or corium may contain sebaceous glands, hair follicles, fat cells, smooth muscle, elastic fibers and blood vessels. Calcification and bony or cartilaginous spicules may occur in the connective tissue matrix and be visible roentgenographically. Although histologically the epidermoids are usually composed of four concentric layers of different thickness, named the stratum durum, the stratum granulosum, the stratum fibrosum and the stratum cellulosum, each of these may become detached and lie free. For this reason they are difficult to fix and section, and the microscopic picture often is ragged and fragmentary. The more external stratum durum, the layer responsible for the pearly sheen, is made up of layers of collagen fibers with little or no trace of cellular formation. The underlying stratum granulosum, essentially a cellular layer composed of stratified to cuboidal epithelium, corresponds with the dermis. Its typical cell is a comparatively large, oval or circular structure with a large rounded nucleus, both of which stain intensely blue with iron hematoxylin. Throughout the cytoplasm are scattered fine granules of keratohyalin, which in the deeper layers of the stratum become larger and more numerous. Between the stratum granulosum and the deeper layers of the tumor, there is usually a sharp line of demarcation and even an actual gap. Although the stratum fibrosum and the stratum cellulosum are the innermost zones of the neoplasm, a clear differentiation between these two strata is often not possible, for the tissue underlying the stratum granulosum seems to pass by gradual transition into the main central mass of the epidermoid. These layers bear some resemblance to the stratum durum and are made up of loosely packed layers of wavy, homogeneous laminae with the staining properties of keratohyalin. It has been felt that a more appropriate name for the tissue constituting the bulk of the tumor would be "area cornea," because of its similarity in appearance and in chemical properties to the most superficial elements of the dermis. In the area cornea are the retention products of cast-off dead and horny scales. The presence of cholesterol crystals is accounted for by the breakdown of keratin and keratohyalin. There is a striking absence of vascularity throughout the whole of the tumor.

With the exception of the cerebellopontile angle and the diploic areas of the skull, the ordinary situations of the dermal and of the epidermal cholesteatomas are similar. They arise for the most part from the subarachnoid cistern somewhere near the midline at the base of the brain or in the region of the fourth ventricle. While one of the most common places for the non-hair-containing variety is in the cerebellopontile angle, few dermoids have been reported in such locations. As Bucy<sup>45</sup> has pointed out, epidermoids may arise beneath the scalp, within the diploe, between the bone and the dura mater and beneath the arachnoid membrane. The less common, slowly accumulating epidermoids between the inner and the outer table of the skull, the intradiploic type, may attain great size and markedly deform one of the cerebral hemispheres without giving neurologic evidence of their presence.<sup>24</sup> On the other hand, few diploic dermoids have been reported. In the growth of an extradural, intradiploic cholesteatoma, the tables of the skull are pushed apart, with absorption of either the inner or the outer table or both, the

45. Bucy, P. C.: Intradiploic Epidermoid (Cholesteatoma) of the Skull, *Arch. Surg.* 31: 190 (Aug.) 1935.

inner table as a rule being more affected. The result is a fairly characteristic roentgenographic picture, with a clear line of demarcation caused by a ridge of the bone forming a rim around the margin of the growth.

The dermoids are usually much larger than the epidermal tumors and have a tendency to push into one or the other cerebral hemisphere, especially in the temporal lobe. They are also much more apt to be cystic and are more frequently single than are the epidermoids.

According to Frank,<sup>46</sup> in the case recorded by Ladame in 1890 three tumors occurred, two in the lateral ventricle attached to the corpus callosum and another nearby. The first reported epidermoid of the spinal cord, that described by Eppinger<sup>47</sup> in 1875, was one of multiple tumors of the cord and brain growing in relationship with the blood vessels. In Trachtenberg's<sup>48</sup> case reported in 1898 there were multiple arachnoid epidermoids and dermoids of the cervical, dorsal and lumbar portions of the cord. Cholesteatomas were likewise found in the left sylvian fossa, in the left frontal lobe, in both lateral ventricles, in the choroid plexuses of the lateral and third ventricles and in the corpora quadrigemina. Microscopically he found them to resemble the tumors described by Bostroem.<sup>2</sup> Other examples were published in 1903 by Ivanoff<sup>49</sup> and in 1904 by Raymond, Alquier and Courtellemont.<sup>50</sup>

With the exception of the diploic epidermoids, the diagnosis and localization of these tumors depend on the same methods used for other intracranial neoplasms. In spite of the fact that the roentgenographic picture of the diploic, or cranial, epidermoids is strikingly characteristic, these tumors are frequently operated on as sebaceous cysts. This is probably accounted for by the fact that the roentgenographic appearance and pathologic characteristics of these tumors are relatively unknown. Love and Kernohan<sup>21</sup> have pointed out that sebaceous cysts of the scalp should be distinguished from epidermoid tumors situated between the scalp and the skull, the greatest difference being an absence of squamous epithelium and of keratohyalin granules and the presence, instead, of a secreting type of epithelium in the former.

Of our series of 11 diploic epidermoids, only 4 were properly diagnosed when first seen. Three of the patients were operated on elsewhere. One of these epidermoids, which had been operated on several times without complete removal, showed suggestive malignant change, sufficient to give the appearance of a squamous cell carcinoma.

As has been emphasized by Cushing,<sup>44</sup> Bucy,<sup>45</sup> King<sup>24</sup> and others, it is important that the wall of the cyst, which is the only living, growing part of the neoplasm, be completely removed. This must be done to prevent recurrence; simple evacuation will not suffice. Because the diploic epidermoids are easily diagnosed, are accessible surgically and usually can be removed entirely, it is important that they be recognized before they reach a size which might make complete removal impossible. A good illustration of the importance of this is evident in case 9.

46. Frank, C.: Ueber einen in der Duerener Irrenanstalt beobachteten Fall von Cholesteatom, *Allg. Ztschr. f. Psychiat.* **46**:30, 1890.

47. Eppinger, H. E.: Mitteilungen aus dem pathologischen anatomischen Institut, Prag., *Vrtljschr. f. d. prakt. Heilk.* **133**:126, 1875.

48. Trachtenberg, M. A.: Ein Beitrag zur Lehre von den arachnoidealen Epidermoiden und Dermoiden des Hirns und Rückenmarks, *Virchows Arch. f. path. Anat.* **154**:274, 1898.

49. Ivanoff, N. S.: Cholesteatom des Rückenmarks, *J. nevropat. i psikhiat. Korsakova (supp.)* **3**:80, 1903.

50. Raymond, F.; Alquier, L., and Courtellemont, V.: Un cas de kyste dermoïde des centres nerveux, *Rev. neurol.* **12**:635, 1904.

Results with the intracranial epidermoids are far less satisfactory. Although, again, complete extirpation should, if possible, be undertaken, often intracapsular enucleation is all that can be accomplished. When the capsule remains recurrence is likely, for it is the capsular portion which constitutes the active, growing portion of the tumor. Because of the neoplasm's avascularity, the contents and capsule occasionally can be removed. Not infrequently, however, the tumor may spread rather extensively along the cisterna interpeduncularis and into the region of the third ventricle. A portion of the capsule may be intimately associated with such structures as the optic nerve or the vessels of the circle of Willis. In such instances complete removal is out of the question.

#### SUMMARY

Dermoid and epidermoid tumors (cholesteatomas) of the central nervous system are uncommon, slowly growing neoplasms representing epiblastic inclusions of the dermal and epidermal layers. The intracranial variety is seldom diagnosed preoperatively. The extradural, or diploic, type can be recognized roentgenographically.

The diploic type is easily accessible surgically, and postoperative results are exceptionally good. Sebaceous cysts of the scalp can be distinguished pathologically from epidermoid tumors by the absence of squamous epithelium and of keratohyalin granules and the presence, instead, of a secreting type of epithelium in the former. The fact that such epidermoids are sometimes overlooked may be given as the reason that Mahoney<sup>3</sup> was able to find only 23 diploic epidermoids in the series of 142 which he collected from the literature in 1936.

Although complete extirpation of these tumors is necessary to prevent recurrence, this often cannot be accomplished in the cases of intracranial epidermoids, because of their extent and attachment to vital structures. The epidermoids of the cerebellopontile angle show signs and symptoms similar to those of acoustic neurinomas, with the exception that there seems to be a greater involvement of the cranial nerves on the affected side.

The use of the words "epidermoid" and "dermoid," suggesting their origin, seems the most satisfactory terminology for these tumors. The term "cholesteatoma" is an unfortunate designation, for the reason that it refers to a chemical by-product which is neither an essential nor an invariable constituent of these tumors.

The history, incidence and pathology of these neoplasms are discussed.

# SO-CALLED "BENIGN METASTASIZING GOITER"

## REPORT OF TWO CASES WITH INTRACRANIAL METASTASIS

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Medical literature contains numerous references to so-called "benign metastasizing goiter" and to "metastasizing normal thyroid tissue." Attention was first drawn to this condition by Cohnheim,<sup>1</sup> who reported such a case in 1876. Many reports have since appeared. In 1926 Simpson<sup>2</sup> reviewed the literature and collected 77 cases. Since that survey 28 additional cases have been reported in the literature.

The ability of tumors to metastasize at a distance has been generally considered a cardinal criterion of malignancy. Nevertheless certain primary benign neoplasms, chiefly those of connective tissue origin, such as lipomas, myxomas and chondromas, are capable of widespread dissemination. Generalization of benign epithelial tumors, on the other hand, rarely if ever occurs.

According to the literature, adenoma of the thyroid gland apparently forms an exception to the rule of nonmetastasization of benign epithelial tumors. Cases of simple adenoma, of hyperplastic goiter and even of normal thyroid tissue with single or multiple implants in distant organs have been reported. Much controversy has raged over this fact, with conflicting opinions as to whether such a situation can exist.

Cruickshank,<sup>3</sup> Symmers,<sup>4</sup> Ginsburg<sup>5</sup> and others have favored the theory of benign metastasis. According to Cruickshank:

A normal thyroid, a colloid thyroid, a thyroid containing a small adenoma, a thyroid containing a malignant adenoma, each has at some time or other been reported as having produced a metastasis consisting of normal thyroid tissue. . . . The clinical fact, or observation, remains that tumours identical with normal thyroid tissue do occur in bones of patients who present no apparent abnormality of their thyroid glands.

Ginsburg, who made a study of metastasis from thyroid tumors to bone, cited a number of cases in support of his contention that metastasis to bone is of frequent occurrence, not only with carcinoma and sarcoma but with simple adenoma of the thyroid gland. He also stated that bulky metastatic tumors of bone, single or multiple, may arise not only from a large primary lesion but from a small, symptomless and histologically benign simple adenoma of the thyroid gland and that even a malignant metastatic tumor may arise from a benign primary adenoma. Symmers<sup>4</sup> regarded some of these metastases as representing aberrant thyroid anlagen which may occur in various parts of the body, including the meninges. Though the tumors are histologically benign, he admitted their ability to assume malignant potentialities, in that they may set up secondary deposits in distant structures.

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1. Cohnheim, J.: Einfacher Gallertkropf mit Metastasen, Virchows Arch. f. path. Anat. **68**:547, 1876.

2. Simpson, W. M.: Three Cases of Thyroid Metastasis to Bones, Surg., Gynec. & Obst. **42**:489, 1926.

3. Cruickshank, M. M.: Thyroid Metastasis in Bone, Indian M. Gaz. **73**:656, 1938.

4. Symmers, D., cited by Kaplan, I. I.: Benign Metastatic Bone Involvement from Thyroid Tumors, Am. J. Surg. **23**:559, 1934.

5. Ginsburg, S.: Bone Metastasis of Thyroid Tumors, Am. J. Roentgenol. **17**:203, 1927.

The opposing view, namely that so-called "benign metastatic thyroid nodules" represent secondary implants from a primary carcinoma of the thyroid gland, is now favored by most authorities. Simpson has been the chief protagonist of this viewpoint, and he has been supported by Shields Warren,<sup>6</sup> Graham<sup>7</sup> and others.

Careful analysis of the cases in the literature reveals that in most instances the diagnosis was based on the clinically benign appearance of the goiter of the thyroid gland and on the benign microscopic appearance of extirpated metastases. In only 29 of the 77 cases studied by Simpson were there microscopic examinations of the thyroid gland, and in many of these there were areas of undoubted carcinoma which went unrecognized. In most instances the authors published case reports shortly after they discovered the innocent microscopic appearance of the metastases without waiting to learn the ultimate fate of the patient. Patients with so-called "benign metastasizing goiter" have many years later died from frank carcinoma of the thyroid gland. Simpson cited 3 cases of his own in point which clearly illustrate the truth of this contention. Many cases are recorded in which the microscopic examination of the tissue from the metastases revealed normal thyroid structure while subsequent histologic study of the thyroid gland itself showed areas of undoubted carcinoma. A similar situation applies to the recently reported cases as well. All in all, therefore, very few of the reported cases can be accepted as instances of "benign metastasizing thyroid tumor." The evidence in these cases rests on the study of the thyroid gland as well as of the metastases. That benign thyroid tumors can metastasize at a distance is postulated on evidence that other primary benign neoplasms are capable of distributing secondary implants at a site removed from the primary lesion.

#### PATHOGENESIS

Of interest are the theories which have been invoked to explain the pathogenesis of this condition.

One theory is that metastases represent misplaced embryonal cells or aberrant thyroid tissue. This is the view held by Ewing,<sup>8</sup> who stated: "In explanation of these cases it seems necessary to assume an origin either from aberrant thyroid tissue or from dislodged cells from the normal thyroid." However, he cautiously added: "Yet in none of these cases has the supposed normal thyroid been submitted to microscopical examination." The presence of multiple widely disseminated foci of thyroid tissue in areas where aberrant thyroid tissue could not possibly occur also invalidates this argument.

A second explanation is that normal thyroid tissue, because of its close relationship to blood and lymph channels, may break into the blood stream, be carried to bone and set up a new growth, bone forming an excellent medium for the growth of thyroid cells. This theory also appears illogical, for if normal thyroid cells possess the power to proliferate in a favorable environment, such as bone, it is strange that artificial autoplasmic implantations of thyroid tissue in long bones have not been followed by such proliferative and destructive growth. Then, too, if normal thyroid cells possess such an unlimited capacity for growth in distant organs, it seems remarkable that metastases should occur so infrequently.

6. Warren, S.: Significance of Invasion of Blood Vessels in Adenomas, *Arch. Path.* **11**:255, 1931.

7. Graham, A.: Malignant Epithelial Tumors of the Thyroid, *Surg., Gynec. & Obst.* **39**:781, 1924.

8. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 987.

The third and most likely view is that the goiter which gives origin to metastases ought not to be considered a benign tumor and that the metastatic tumors arising from it, even though histologically not malignant, should be considered as such.

The evidence for this third view is as follows:

1. The vast majority of reported cases cannot be accepted because only a few of the so-called "normal thyroids" or "benign goiters" have been submitted to microscopic examination and only a few of the thyroids examined histologically have been studied adequately to rule out malignancy.

2. The metastases of so-called "benign goiters" show the same predilection for bone that characterizes secondary carcinomatous implants. The cranial bones, the sternum, the vertebral bodies, the humerus and the femur are the most frequent sites, in the order named.

3. According to the opinion of the most authoritative pathologists, the morphologic character of the tissue is an unreliable basis for the determination of malignancy of thyroid epithelial tumors. There is even considerable variation in architecture in a single portion of normal thyroid tissue.

Graham<sup>7</sup> categorically stated: "Epithelial tumors of the thyroid gland that are encapsulated and show no blood vessel invasion are benign irrespective of their microscopic picture. Epithelial tumors that invade the capsule or blood stream are malignant irrespective of the microscopic appearance." Furthermore, the primary malignant lesion in the thyroid may be miniature and escape clinical and even microscopic detection unless serial sections are made.

#### CLINICAL FEATURES

Clinically, these lesions are insidious in onset and do not present symptoms different from those of other tumors of bone. However, two interesting observations that are of diagnostic importance are the presence of palpable and often visible pulsations synchronous with the pulse and the tendency of the metastases to fluctuate in size during menstruation and pregnancy. Pulsation is especially common in cranial metastases, and a bruit is not infrequently audible over the mass. Another interesting feature is that the metastatic implants may function, with resultant hyperthyroidism. Oddly enough, removal of the primary lesion rarely produces changes in symptoms, but removal of the secondary growth may cause relief of symptoms and even myxedema.

The true nature of the lesion remains unsuspected as a rule until the pathologist has reported his observations. According to Zadek,<sup>9</sup> approximately 38 per cent of the bone metastases are in the cranium and 15 per cent in the vertebrae. Two thirds to three quarters of the patients are females. The average age is 40 to 60 years. The condition is often of many years' duration.

#### TREATMENT

Concerning treatment, radical surgical removal of metastatic thyroid tissue if accessible, as well as of the primary tumor, is indicated, especially because of the almost universal and sometimes fatal recurrences. Fortunately these are not apt to appear until several years has elapsed. In some of the reported cases extirpation of the metastatic tumor resulted in permanent cure. This is the exception rather than the rule. Roentgen therapy to the site of metastatic implants and to the

9. Zadek, I.: Pathological Fracture of Neck of Femur Due to Thyroid Metastases, *Ann. Surg.* 77:689, 1923.

thyroid gland itself is indicated whenever possible, because of the radiosensitiveness of these neoplasms.

Two illustrative cases are reported.

#### REPORT OF CASES

M. S., a 51 year old housewife, was admitted to the Jewish Hospital of Brooklyn, service of Dr. Leo M. Davidoff, on Jan. 25, 1942, because of progressive exophthalmos in the right eye of three months' duration. There was some blurring of vision of the right eye on occasions,



Fig. 1 (case 1).—Thyroid tissue in temporal bone resembling benign adenoma with destruction of bone (hematoxylin and eosin stain;  $\times 250$ ).

especially during reading, but no other visual symptoms. She had suffered from migraine during the past thirty years. Otherwise her past history was irrelevant.

Significant findings on physical examination were limited to the eyes. There were exophthalmos and defective abduction and elevation of the right eye, slight dilatation of the right pupil and slight pallor of the extreme temporal margin of the right optic disk. The visual fields were normal. The neurologic examination gave entirely negative results.

Roentgenograms of the skull revealed a destructive process involving the right sphenoid ridge and the posterior portion of the right orbit with marked decalcification. Along the outer portion of the ridge, adjacent to the skull table, was a calcific deposit, believed to be part and parcel of the tumor mass. Both optic foramina were normal. These observations

were considered as consistent with the diagnosis of a tumor in this region involving the skull, possibly a meningioma of the sphenoid ridge.

Operation was accordingly performed on January 27 by Dr. Davidoff. It revealed an extensive, exclusively extradural tumor involving the squamous portion of the temporal bone, the lesser wing of the sphenoid and the orbital roof and fascia on the right side. In places the tumor had eroded through the temporal bone and made its way into the temporal fossa beneath the temporal muscle. It was felt that the tumor was either a meningioma or a sarcoma. A total gross removal of the tumor was carried out.

The patient seemed to be in fairly good condition for about thirty-six hours after the operation. She then began to complain of pain in the face and in the right eye and became drowsy slowly. The drowsiness increased, and she eventually became comatose. Her right



Fig. 2 (case 1).—Section from thyroid gland with fetal adenoma (hematoxylin and eosin stain;  $\times 250$ ).

pupil became dilated as compared with the left, her pulse became slower and her blood pressure rose. A diagnosis of extradural hematoma was made. Immediate operation was performed; the diagnosis was verified, and the freshly accumulated extradural clot was evacuated through the operative site. Thereafter she made slow but steady progress and her course was uneventful. The exophthalmos receded considerably.

To the amazement of every one concerned, the tumor was reported histologically as composed of thyroid gland tissue (papillary adenoma), evidently metastatic (fig. 1). There was no histologic evidence of malignancy, nor were tumor cells seen within blood vessels. Careful reexamination of the patient then revealed a small nodule in the left lobe of the thyroid gland. It was felt that the metastatic deposit probably arose from this nodule, and its removal was deemed advisable. The basal metabolic rate as determined on February 13 was reported to



be +19; however, the patient was extremely restless on that day and the report was considered unreliable, especially since her basal metabolic rate prior to admission was reported as normal by the family physician.

On February 18 subtotal thyroidectomy was performed by Dr. H. Louria. The thyroid gland weighed 23 Gm. The left lobe contained two well encapsulated nodules, the larger of which measured 3 cm. in diameter. The left lobe contained a solitary small nodule. All resembled fetal adenomas. Histologically the thyroid gland and the adenomas appeared benign, with orderly arrangement of cells (fig. 2). No evidence of intracapsular extension or invasion of blood vessels was found. The microscopic diagnosis was adenomas of the thyroid gland.



Fig. 3 (case 2).—Section of tumor from frontal bone resembling fetal adenoma (hematoxylin and eosin stain;  $\times 250$ ).

The patient was discharged on February 20, evidently having made a satisfactory recovery from both operations.

Laboratory data were essentially within normal limits.

The patient is now receiving roentgen therapy to the skull and neck, and thus far there is no evidence of recurrence or further metastases.

The final diagnosis was so-called "benign metastasizing goiter" with metastases to skull and probably carcinoma of the thyroid gland.

CASE 2.—D. J., a 57 year old Jewish housewife, was admitted to the Jewish Hospital of Brooklyn, service of Dr. Leo M. Davidoff, on March 19, 1942, because of a lump on the right

side of her skull in the frontal region. The lump had been present for a year, but she had paid little attention to it until shortly before admission, when she noted that it had become progressively larger. She also noticed the presence of a dilated blood vessel in proximity to the mass and was aware of pulsation of that vessel. She said she had not felt any pain in this region, and neurologic inquiry gave negative results. She had had a laparotomy thirty-four years previously, reportedly for an "abscess," and had known of a lump in her neck for twenty years. Two days before admission she came to the outpatient department and was told she had a cyst and advised to return on the day of admission for excision of the mass. This was attempted with local anesthesia, but after the initial incision had been made unusual



Fig. 4 (case 2).—Section with thyroid tissue in lumen of vein in thyroid gland.

vascularity and pulsation of the mass were noted. The wound was immediately sutured, and hospitalization was advised.

When the patient was admitted to the hospital a plum-sized mass over the right frontal area pulsated visibly. A bruit was readily audible over the right frontotemporal region, and a greatly dilated temporal arterial vessel was noted. It was the opinion of one examiner that pressure over the right carotid artery caused the mass to cease pulsating and obliterated the bruit. The thyroid gland presented a bilateral nodular enlargement. The right lobe was somewhat larger than the left. According to the patient, the mass in the right lobe was of recent origin and the nodule in the left lobe was of many years' duration. Both lobes, however, were movable and did not appear to be adherent to the underlying tissue. Clinically the

thyroid gland did not appear to contain any malignant growth. A suprapubic incisional hernia and advanced bilateral varicosities of both lower extremities were noted.

Roentgenograms of the skull showed a large defect in the right frontal bone, measuring 5 by 4 cm., with irregular, serrated edges. There was considerable increase in the number of vascular channels inferior to the lesion.

The patient was discharged on March 24 and advised to return when the cutaneous incision made when she was being treated in the outpatient department had healed.

She returned on May 4. Operation was performed on May 6 and revealed a pink-gray, meaty, vascular friable mass deep to the pericranium in the right frontal region with a bony defect. A frozen section of biopsy material from the tumor was reported as benign thyroid adenoma. The tumor was partially resected with the electrocautery. Hemostasis was obtained with difficulty.

Grossly, the tumor consisted of a spherical mass of tissue which weighed 22 Gm. and measured 5.3 by 5 by 1.7 cm. One surface appeared smooth and glistening and was pink-gray; the other surface was fairly homogeneous, dry and opaque. In places the tumor had a lobulated appearance. The central portion was dense and firm. Microscopically the tissue resembled a simple adenoma of the thyroid gland (fig. 3). It betrayed none of the characteristics usually associated with malignant growth.

The wound healed per primam intentionem. Roentgenograms of the long bones, the spine and the chest failed to disclose any evidence of metastatic malignant growth. Her basal metabolic rate was  $\pm 7$ . It was felt that this case also was one of so-called "benign metastasizing goiter," and removal of the primary growth was deemed advisable. Subtotal thyroidectomy was accordingly performed on May 20, with local anesthesia.

Grossly the thyroid gland weighed 70 Gm. and measured 8 by 6 by 4 cm. The entire specimen consisted of two distinct encapsulated nodules attached to one another by a thin bridge of thyroid tissue. The consistency of the tissue was firm; calcification was noted in some areas. The cut surfaces of the larger nodule presented central areas of cavitation with fresh hemorrhages. The peripheral zone was homogeneous, opaque and pale gray and contained irregular calcific deposits. The smaller nodule was similar. Microscopic examination revealed that the nodules were adenomas (fig. 4). In some areas, however, there were evidences of malignancy in the form of abnormal cell structure, hyperchromatosis, mitotic figures, irregularities of cell growth and invasion of blood vessels. The histologic diagnosis was carcinoma and adenoma of the thyroid gland.

Other laboratory data were essentially normal.

The patient made a satisfactory recovery from both operations, was discharged on May 29 and is now receiving roentgen therapy to her skull.

The final diagnosis was carcinoma and adenoma of the thyroid gland with metastases to the right frontal bone.

#### COMMENT

The first case falls very nicely into the category of "benign metastasizing goiter." Yet in spite of the benign histologic appearance of both the primary lesion and the secondary lesions, the condition is to be regarded as malignant. The presence of secondary deposits in the skull indicates that invasion through blood vessels had taken place at some time in the history of the primary thyroid neoplasm. This is *prima facie* evidence of malignancy. As has been noted, the histologic structure is of little importance in the determination of malignancy of thyroid tissue. It is also possible that serial sections of the thyroid gland might have uncovered a miniature area of carcinoma. Such examination was not feasible in this case because of technical difficulties. Several blocks were studied however.

The second case is illustrative of the fact that metastases from thyroid carcinoma may bear little or no resemblance to the primary lesion and that unless the primary tumor is also studied, the true nature of the condition remains unrecognized. Because of the clinically benign appearance of the thyroid gland and the benign histologic character of the cranial tumor, this case would undoubtedly have been recorded in the older literature as one of metastasizing thyroid adenoma. The tumor's pulsatile nature and the audible bruit are in keeping with the well recognized clinical features of these lesions.

## SUMMARY AND CONCLUSIONS

The literature of so-called "benign metastasizing goiter" is briefly reviewed.

In spite of the histologically benign appearance of the primary tumor or the metastases or both, the condition is to be regarded as malignant.

Two cases illustrating the outstanding clinical and pathologic features of this condition are reported.

Intracranial neoplasms in patients with goiters should be considered metastatic until proved otherwise, even though the thyroid lesion appears to be insignificant.

Treatment consists of radical surgical removal of the primary and secondary lesions followed by roentgen therapy.

# THE SOLID CARBON DIOXIDE-FERRIC CHLORIDE TECHNIC FOR HEMOSTASIS

## EXPERIMENTAL STUDY OF ITS EFFECTIVENESS IN BRAIN, VISCERA AND SUPERIOR SAGITTAL SINUS

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A new technic has been developed with experimental animals for the control of bleeding from the cross-sectional surfaces of vessels in the brain and the viscera, as encountered after excision of blocks of tissue, and from lacerations of the superior sagittal sinus. At this time this procedure may have special application in war surgery.

In a report on a new method of excising blocks of brain tissue with minimal bleeding by means of liquid nitrogen and a mechanical device, Koskoff and his associates<sup>1</sup> stated: "The slight hemorrhage which usually follows the removal of the instrument is easily controlled by pouring a small amount of liquid nitrogen into the bleeding area. This congeals the blood and a dry crater remains." In an earlier paper<sup>2</sup> I have discussed the effects of low temperature freezing on cerebral and vascular tissues. This type of refrigeration preserves cell structure; the tissues return to normal on thawing. Therefore, low temperature freezing can be expected to act only as a temporary hemostatic. In order to corroborate this theory, a block of tissue was excised from the brain of a cat and liquid nitrogen was applied to the oozing vessels in the crater. The area was frozen, and bleeding stopped. Within about thirty seconds, when thawing had taken place, bleeding began again. It appears, then, that freezing with liquid nitrogen or solid carbon dioxide can act only as a temporary hemostatic.

The possibility of utilizing refrigeration with liquid nitrogen or solid carbon dioxide as a preliminary to chemical coagulation for permanent hemostasis presented itself. Styptics alone are relatively ineffective, because they are readily diluted and washed away by flowing blood. Preliminary refrigeration stops blood flow temporarily, freezing the accumulated blood and the mouths of the vessels; a chemical coagulant might then be applied and bleeding be stopped permanently.

Liquid nitrogen and solid carbon dioxide were considered as freezing agents. Liquid nitrogen was both sprayed and poured on bleeding areas of brain and liver. It was found that bleeding of more than minimal degree prevented refrigeration, because the freezing liquid was washed away. On the other hand, blocks of solid carbon dioxide applied with moderate pressure were in all cases effective in freezing the bleeding area.

Various chemical coagulants were tested, including silver nitrate, tannic acid, zinc chloride, copper sulfate, aluminum sulfate, potassium aluminum sulfate, iron ammonium sulfate, and ferric chloride. Of these a 20 per cent solution of ferric

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1. Koskoff, Y. D.; Markson, V., and Wall, N. M.: Method for Removal of Areas of Brain Following Freezing in Situ, *Am. J. Surg.* 50:271-273, 1940.

2. Ebin, J.: The Carbon Dioxide Snow-Electrocautery Technique for Occlusion of Large Veins: Suggested Application to Venous Angioma of the Brain, *Surg., Gynec. & Obst.* 76:43-50, 1943.

chloride was found most effective. Ferric chloride combines with proteins, principally those of the plasma (albumin, globulin and fibrinogen), to form ferric proteinate, a black coagulum which occludes the mouths of the torn vessels.

Methods of handling and shaping the refrigerant have been previously presented.<sup>2</sup> It is a white solid having a temperature of  $-78^{\circ}\text{C}$ . and may be kept in a vacuum jar, from which there is a loss of 5 per cent per day. The material is surrounded by a film of gas which acts as an insulator and must be removed by pressure before freezing can occur. Solid carbon dioxide is bacteriologically sterile. Blocks are cut with a hack saw. Smaller pieces are formed with a hammer and a moderately keen-edged knife. Narrow wedges are cut with a heated knife blade used with a sawing motion.

The refrigerant must come in contact with all bleeding points for coagulation to be fully effective. The solid carbon dioxide must therefore approximately fit the bleeding area; various shapes may be necessary. For flat surfaces, blocks of solid carbon dioxide are satisfactory. For craters, such as are seen after excision of blocks of cerebral tissue, rounded presenting surfaces are best. Such a surface is made by rounding off the sharp corners of a square presenting surface with the flat of a knife blade heated in a Bunsen flame. For use in lacerations, such as may occur in the liver, narrow wedges are most satisfactory, since they permit freezing of vessels in the deepest part of the tear. Various sizes and shapes of solid carbon dioxide are prepared before operation and kept in a vacuum jar until needed. A small sterile knife is kept on the instrument table to make minor changes in the shape of the solid carbon dioxide as required. An Allis clamp, or a large curved clamp with close-fitting rubber tubing on the prongs, is used to handle the refrigerant.

Ferric chloride is obtained in crystalline form, and a 20 per cent solution in distilled water is made up. The solution is then passed through filter paper. It has a  $p_{\text{H}}$  of 1 and is therefore bacteriologically sterile. Repeated efforts to grow organisms from it, with agar, blood agar, broth, blood broth and anaerobic meat broth as culture mediums have failed.

The ferric chloride solution is best applied by means of absorbent cotton. Johnson and Johnson absorbent cotton pellets, medium size, no. 2, are used, but any form of this material is satisfactory. Dental rolls are unsatisfactory as they do not readily give up the solution. A suction tip of large caliber is used.

The best results are obtained when the suggested technic is closely adhered to.

#### BRAIN

Various methods are now in use for the control of bleeding from the cross-sectional surfaces of blood vessels in the brain. Horsley<sup>3</sup> first suggested the application of small pieces of muscle to bleeding points. Cushing<sup>4</sup> introduced the silver clip and was the first to use the electrocautery<sup>5</sup> in neurosurgery. Dry absorbent cotton or absorbent cotton moistened in warm saline solution is also helpful. Frequently, however, these are not adequate, and hemorrhage becomes a serious problem.

3. Horsley, V.: Note on Hemostasis by Application of Living Tissue, *Brit. M. J.* 2:8, 1914.

4. Cushing, H.: The Control of Bleeding in Operations for Brain Tumors, with the Description of Silver "Clips" for the Occlusion of Vessels Inaccessible to the Ligature, *Ann. Surg.* 54:1-19, 1911.

5. Cushing, H., and Bovie, W. T.: Electrosurgery as Aid to Removal of Intracranial Tumors, *Surg., Gynec. & Obst.* 47:751-784, 1928.

The solid carbon dioxide-ferric chloride technic has been used successfully for the control of bleeding in the brains of 12 cats and 4 dogs. Alexander and Putnam<sup>6</sup> have divided cerebral blood vessels into seven types according to caliber. Types 7, 6 and 5 include the internal carotid, the middle cerebral and the anastomosing pial vessels; types 4, 3, 2 and 1 comprehend all intracerebral branches, type 4 representing the penetrating vessels, types 3 and 2 representing the branches resulting from the next two subdivisions and type 1 representing the capillaries. These authors stated: "In spite of the great differences in size of the body and brain, the intracerebral blood vessels of fourth, third, second and first orders are of approximately similar size in the human being, the cat, the guinea pig and the pigeon." The caliber of intracerebral vessels in the experimental animal thus closely approximates the caliber of those in man. Bleeding from pial vessels, which are larger in the human being, may be controlled by silver clips.

The tissue removed from cats has on the average measured 1 cm. in diameter and 0.5 cm. in thickness; that from dogs, 2 cm. in diameter and 0.5 cm. in thickness. Pieces of solid carbon dioxide of approximately the same size with a rounded presenting surface have been used, the depth being greater than that of the excavation to allow room for grasping the material with a clamp. For larger areas, pieces with presenting surfaces 2.5, 3, 3.5 or 4 cm. in diameter may be used.

A wide exposure of brain is obtained, and the scalp, muscle, bone and dura are walled off with flat cotton strips in order to prevent contact with the ferric chloride solution. The removal of a block of tissue from the brain is followed by brisk bleeding. The solid carbon dioxide is applied with moderate pressure, care being taken that contact is made with all bleeding points. It sometimes requires manipulation of the refrigerant in order to touch and freeze all these points. While the refrigerant is in place, the pial vessels bordering on the area are clipped and cotton strips are placed on the adjacent cortex. After the area has been frozen for one minute the refrigerant is removed. The frozen area is seen to be covered with a white frost. Cotton pellets soaked in ferric chloride solution are then placed on the frozen part for one minute. At the end of this time the pellets are carefully taken off, and the excess solution is removed by suction. The treated area is seen to be covered with a black coagulum of ferric proteinate about 0.3 mm. in thickness (figure). If blood seeps through the ferric chloride pellets, the pellets are removed. The area is irrigated and suction is used in order to locate the bleeding points, and freezing and coagulation are repeated.

In most cases the technic has been successful on the first attempt. In a few experiments several repetitions have been required, but in every instance bleeding was stopped. The most frequent cause for the necessity of repetition has been failure to touch deep bleeding points with the refrigerant. A second cause, which stems from the difficulty of adequate exposure in relatively small animals, has been the occasional flow of blood from some source outside the excised area onto the frozen brain. This tends to dilute and wash away the ferric chloride solution.

Care must be exercised to avoid pushing the refrigerant into a ventricular cavity, since in this situation carbon dioxide gas is given off by the solid carbon dioxide and the cavity is expanded. This is particularly likely to happen in the brains of small animals, such as the cat, because the layer of tissue external to the ventricle is relatively thin. *Therefore, if the bleeding area communicates with or is directly adjacent to a part of the ventricular system, the procedure is not used.*

6. Alexander, L., and Putnam, T. J.: Pathological Alterations of Cerebral Vascular Patterns, A. Research Nerv. & Ment. Dis., Proc. (1937) 18:471-543, 1938

In a previous report<sup>2</sup> the effects of low temperature freezing on brain tissue were considered in detail. The conclusions reached were that low temperature freezing in itself does not injure tissue, that the damage following refrigeration with solid carbon dioxide is the result of pressure and that this damage is superficial and negligible. The effects of ferric chloride alone and of solid carbon dioxide and ferric chloride on cortical and subcortical tissue were studied. Two cats were treated with cotton pellets soaked in a 20 per cent solution of ferric



Bleeding from a crater in the brain of a cat stopped by the use of solid carbon dioxide and ferric chloride ( $\times 1$ ): A, bleeding; B, frozen; C, ferric chloride pellets in place; D, crater covered with coagulum and bleeding stopped.

chloride applied to an area of cortex 1 cm. in diameter for one minute. When the pellets were removed a pale tan discoloration was visible in the treated area. The surrounding brain tissue was normal in appearance. The cats were normal during a period of three weeks, at the end of which they were killed. At autopsy the same pale tan discoloration was noted. There was no evidence of infection or sterile reaction. Cross section revealed no injury. Microscopic examination



showed absence of the pia-arachnoid in parts of the treated area and occasional small areas of fibrosis in the zonal layer of the cortex.

A piece of solid carbon dioxide 1 cm. in diameter was applied with moderate pressure to an area of cortex in each of 2 cats for one minute, and then cotton pellets soaked in a 20 per cent solution of ferric chloride were placed on the same area for the same length of time. On removal a pale tan discoloration was seen. No abnormality could be detected in the behavior of the animals during the post-operative period of three weeks, at the end of which they were killed. Autopsy disclosed no evidence of infection or sterile reaction. On cross section there was no gross evidence of damage. Microscopic examination in 1 case disclosed normal gray and white matter except for a minute area 1 mm. wide and 0.6 mm. deep in one section. In this area cortical tissue was replaced by fibroblasts, lymphocytes and fat granule cells. In the second specimen a similar picture was seen.

Pieces of tissue were removed from the brains of 2 dogs. Bleeding was stopped by means of solid carbon dioxide and ferric chloride. The animals were normal throughout the postoperative period. At the end of three weeks they were killed. Bleeding had not recurred, and there was no evidence of infection or sterile reaction. Cross section revealed that the excised area had been replaced by fibrous tissue. Surrounding tissues were of normal appearance. Microscopic examination in both cases showed fibrous tissue, lymphocytes and fat granule cells in the area of excision. Adjacent nerve tissue was normal.

The procedure described has been effective in stopping bleeding from the cross-sectional surfaces of vessels in the brains of experimental animals. There has been no recurrence of bleeding, and the damage done by the procedure has been insignificant. This technic may be similarly effective in the control of bleeding from nerve and tumor tissue in the brain of the human being.

#### VISCERA

Bleeding from the liver may occur in the course of a surgical procedure, such as resection for removal of neoplasm, or as the result of trauma. Traumatic lesions are of two types. In the first the abdominal wall is intact, injury being the result of a contusing force. From this type of injury several varieties of damage to the liver may result. There may be lacerations, most frequently sagittal, affecting the convex surface and extending for a varying distance into the depth of the organ; the right lobe is more commonly affected. There may be a subcapsular hematoma without laceration of the capsule, or there may be damage in the depths of the organ with the formation of a central hematoma. In the second type of trauma to the liver lesions are produced by cutting instruments which tear through the abdominal wall. Such lacerations are usually the result of stab wounds and injuries due to firearms.

The generally favored methods of controlling bleeding from the liver are suture and tamponade. Mattress sutures of thick catgut on round blunt needles are favored. Suture with catgut soaked in tissue extracts has also been reported by Dainelli.<sup>7</sup> The friability of the tissues of the liver tends to make this method of controlling bleeding from the liver ineffective. Packing with gauze is on the whole the most reliable method; the gauze may first be soaked in a hemostatic solution. The tampon is left in place for from two to twelve days. Infection and recurrence of hemorrhage on removal of the packing are not infrequent. Additional methods of hemostasis include the use of heated air, water vapor, the actual cautery, omentum, fat, muscle, bone powder, tissue extracts, epinephrine

7. Dainelli, M.: Ricerche sperimentali sull'uso di estratti di tessuti a scopo emostatico, *Ann. ital. di chir.* 13:989-1032, 1934.

and gelatin. Marcucci<sup>8</sup> and Cué<sup>9</sup> have reported on the experimental use of a gum, tragacanth.

Shedden and Johnston<sup>10</sup> reported a case of traumatic laceration of the liver in which bleeding was controlled by gauze packing. In Christopher's<sup>11</sup> case bleeding from the liver was controlled by gauze packing, which was removed on the eighth postoperative day. Removal of the gauze was followed by the development of a subphrenic abscess which required rib resection for drainage. The patient had two episodes of acute intestinal obstruction which required laparotomies with prophylactic enterostomies. Branch<sup>12</sup> and Pickworth<sup>13</sup> were able to control bleeding from traumatic lacerations of the liver by use of mattress sutures.

The solid carbon dioxide-ferric chloride technic has been used successfully in lacerations of the liver in 12 cats and 2 dogs. Bleeding from lacerations in this organ arises from large branches of the hepatic artery, the hepatic vein and the portal vein and from the small vessels of the parenchyma. In these experiments bleeding from all vessels has been stopped. The large vascular trunks are naturally of greater size in the human being. Bleeding from these vessels might be controlled by use of clamp and ligature.

The procedure has been used on areas of the liver from which a section of the surface has been removed and on lacerations extending into its depth. For surface wounds blocks of solid carbon dioxide of approximate size are satisfactory. For lacerations wedges of the refrigerant have been found more effective, since their shape permits contact between the dry ice and the deepest bleeding points. The incisions have been 4 cm. in length, with a greatest depth of 0.8 cm. Wedges used have been of a length and depth greater than that of the laceration to assure contact between the refrigerant and bleeding tissue throughout the entire extent of the tear and to allow room for grasping the material with a clamp. Those used in these experiments have been 5 cm. long, 2.5 cm. thick and 1 cm. wide, the angle of the sides being approximately 22 degrees. Larger wedges may be used for larger lesions. Where slight changes are necessary to make the shape of the refrigerant conform to that of the lesion, they may be made with a knife. In bleeding areas of different form, such as might result from the excision of a block of tissue, a piece of solid carbon dioxide of approximately the same shape may be molded in the manner described previously for use in operation on the brain.

As an example, the procedure in the case of a laceration may be considered. To expose the liver a right pararectus upper abdominal incision is made. The sides of the wound are walled off with gauze to prevent contact with the dry ice or the ferric chloride solution. An incision is made in the liver with a scalpel. A wedge of solid carbon dioxide is inserted into the laceration, and moderate pressure is applied. At the same time the sides of the tear are compressed manually against the refrigerant either from behind or laterally. Manipulation of the refrigerant is sometimes required in order to freeze all bleeding points. While the refrigerant is in place flat cotton strips are placed on the adjacent liver tissue. After the bleeding surfaces have been frozen for one minute, the refrigerant is removed. The frozen area is seen to be covered with a white frost. Absorbent cotton pellets

8. Marcucci, G.: L'emostasi epatica: Ricerche sperimentali, Arch. ital. di chir. **50**:101-119, 1939.

9. Cué, V. B.: Hemostasia hepática: El tuffon. Rev. méd. de Rosario **31**:148-152, 1941.

10. Shedden, W., and Johnston, F.: Traumatic Rupture of Liver, New England J. Med. **213**:960-965, 1935.

11. Christopher, F.: Rupture of Liver, Ann. Surg. **103**:461-464, 1936.

12. Branch, C. D.: Injury of Liver: Report of Two Cases, Ann. Surg. **107**:475-477, 1938.

13. Pickworth, M. E.: Traumatic Rupture of Liver: Report of Case, California & West. Med. **51**:328-329, 1939.

soaked in ferric chloride solution are then placed on the frozen part for one minute. At the end of this time the pellets are carefully taken off and the excess solution is removed. The treated area is seen to be covered with a black coagulum of ferric proteinate. If blood seeps through the pellets they are removed and the entire procedure is repeated. Often the procedure had to be repeated several times in order to stop all bleeding, but in every case the flow of blood was stopped. It has not been necessary in these experiments to clamp and ligate any of the large vascular trunks.

The effects of the application of dry ice and ferric chloride to hepatic tissue were studied in long term experiments. With each of 3 cats a piece of solid carbon dioxide 1 cm. square was applied with moderate pressure to the liver for one minute. On removal of the refrigerant a white frost was seen on the frozen surface, which thawed after about one minute. A dark red discoloration was then noted at the site of freezing. The animals were entirely normal during the postoperative period. At the end of three weeks autopsy revealed no evidence of infection or sterile reaction in the liver or the abdominal cavity. A gray discoloration was seen on the surface of the area which had been frozen. On section this discoloration was apparent to a depth of 1.5 mm. Microscopic examination showed that in the discolored area hepatic tissue had been replaced by fibrous tissue, lymphocytes, blood pigment and fat cells. Surrounding tissue was normal. The mildness of damage conforms with the results of low temperature freezing of brain tissue.

Cotton pellets soaked in ferric chloride solution were applied to the livers of 3 cats for one minute. On their removal a gray discoloration was seen over the treated area. The animals were normal during the postoperative period. Autopsy at the end of three weeks showed no evidence of infection or sterile reaction in the liver or abdominal cavity, nor were there any adhesions. On section through the treated area there was no gross evidence of damage. Microscopic examination revealed detachment of the capsule of the liver in the areas treated. All other structures were normal.

Incisions were made in the livers of 3 cats. Bleeding was stopped by the use of solid carbon dioxide and ferric chloride. During the postoperative period the animals were normal. Autopsy three weeks later showed that there had been no recurrence of bleeding, nor was there evidence of infection or sterile reaction in the liver or abdominal cavity. The only adhesion noted had formed between the treated site and the anterior abdominal wall in 1 animal which had been well and active during the postoperative period. All specimens showed a gray discoloration over the treated surface. On section the line of incision was seen to be occupied by fibrous tissue. On microscopic examination fibrous tissue and collections of lymphocytes were seen in this area. Surrounding tissue was normal.

The solid carbon dioxide-ferric chloride procedure has also been successful in controlling bleeding from lacerations of the lung in cats, and from the spleen and the kidney in both cats and dogs.

Through use of this technic bleeding in the viscera of experimental animals has been stopped. There has been no recurrence of bleeding, and the damage done by the procedure has been negligible. This method of hemostasis may be successful in controlling parenchymatous bleeding from the liver, as well as the lung, the spleen, the kidney, the thyroid and the pancreas in the human being.

#### SUPERIOR SAGITTAL SINUS

Lacerations of the superior sagittal sinus may occur in the course of an operative procedure or as the result of a depressed fracture of the vault of the skull near the midline. The sinus walls contain no elastic tissue and are held rigidly open by

the pull of the dura mater. For this reason bleeding from a torn superior sagittal sinus may be very severe. In lacerations resulting from depressed fractures bleeding may occur immediately or the bone fragment may plug the opening. However, hemorrhage does occur when the fragment of bone is elevated at operation. Loss of blood in these cases may be severe and even fatal.

Methods now in use for the control of bleeding from the superior sagittal sinus include application of slabs of muscle to the tear, packing with gauze, passage of ligatures around the sinus, suture of the tear and application of hemostatic clamps. Slabs of muscle may be successfully used for small wounds but are not effective in larger lacerations even when held in place with dural sutures running across the sinus. Gauze packing is not always adequate for control of bleeding from large tears. Furthermore, when the gauze is removed there is always the danger of recurrence of hemorrhage. Passage of ligatures involves the danger of lacerating the underlying brain, nor is it always successful, since the triangular shape and rigid walls of the sinus resist occlusion by ligature. Suture of the tear with fine silk is difficult in the presence of bleeding. The removal of hemostatic clamps may be accompanied by severe hemorrhage.

Bailey<sup>14</sup> reported a case in which a small tear was controlled with a piece of muscle. In Chavanne's<sup>15</sup> case hemorrhage was arrested by a tampon left in place for six days. Removal was accomplished without bleeding. Bleeding from the superior sagittal sinus was stopped by Bagley<sup>16</sup> with gauze packing. Carlucci<sup>17</sup> encountered severe bleeding which packing did not stop. Suture-ligatures about the sinus anterior and posterior to the tear finally arrested the hemorrhage.

The solid carbon dioxide-ferric chloride procedure has been used successfully in lacerations of the superior sagittal sinus in 5 dogs. In each case a coagulum of ferric proteinate formed over the tear and bleeding stopped. These sinuses measured from 0.3 to 0.35 cm. at their widest point, as compared with about 1 cm. in man.

The principle underlying this procedure is much the same as that described for elimination of cross-sectional bleeding in the brain and in the liver. The flow of blood is temporarily stopped by freezing the torn sinus and the entering superior cerebral veins on each side. The ferric chloride solution may then act on the lacerated surface without being diluted or washed away.

A wide exposure of the sinus is obtained, after which it is torn for its entire width with a no. 11 Bard-Parker blade. A block of solid carbon dioxide 4 cm. long, 4 cm. thick and 2 cm. wide is then applied with moderate pressure to the bleeding sinus. A similar piece is then placed on each side of it in order to freeze the entering superior cerebral veins. While the refrigerant is in place the surrounding scalp, muscle, bone and dura are walled off with gauze and cotton strips. After one and a half minutes the refrigerant is removed, and absorbent cotton pellets soaked in 20 per cent ferric chloride solution are applied to the area of laceration. At the end of one and one-half minutes these are removed. The treated area is seen to be covered with a black coagulum of ferric proteinate. If bleeding recurs while the cotton pellets are in place they are removed and the procedure is repeated. In 3 cases the technic was successful on the first attempt, and in the remaining 2 cases several repetitions were necessary. No convulsions were noted during freezing.

14. Bailey, P.: Wounds of Superior Longitudinal Sinus. *S. Clin. North America* 9:395-405, 1929.

15. Chavanne, F.: Hémorragie du sinus longitudinal supérieur. *Oto-rhino-laryng. internat.* 16:231-232, 1932.

16. Bagley, C., Jr.: Traumatic Longitudinal Sinus Lesions: Report of Two Cases, *Surg., Gynec. & Obst.* 58:498-502, 1934.

17. Carlucci, G. A.: Injury to Longitudinal Sinus Accompanying Depressed Fracture of Skull, *Am. J. Surg.* 45:120-124, 1939.

but in 2 animals occasional temporary apnea for from ten to fifteen seconds was observed while the dry ice was in place. In each case respirations returned to normal.

Two of these animals were allowed to live for three weeks. After the first few days they were alert and active. They showed no symptoms or signs of cerebral damage. At autopsy there was no evidence of recurrence of bleeding or of infection or sterile reaction. In one specimen the sinus was occluded by fibroblasts; in the other, blood pigment was seen. The cortex of the most medial gyrus on each side was replaced by fibrous tissue and fat granule cells to a depth of 1.5 mm. Tissue below that was normal. In the human cortex, whose greatest depth is 4 mm. in the motor area, such damage should in most instances be negligible.

The solid carbon dioxide-ferric chloride procedure has been successful in stopping bleeding from lacerations of the superior sagittal sinus in dogs. Bleeding has not recurred, and damage has been slight. The technic may perhaps be effective in controlling bleeding from lacerations of the superior sagittal sinus in the human being.

#### SUMMARY

A technic for the control of bleeding from the cross-sectional surfaces of vessels in the brain and the viscera and from lacerations of the superior sagittal sinus has been developed with experimental animals. This procedure may be effective in similar situations in human beings and may be of value in war surgery.

Dr. Tracy J. Putnam, in whose laboratory this work was done, gave aid and encouragement.

# TREATMENT OF ACUTE ARTERIAL OCCLUSION BY MEANS OF INTERMITTENT VENOUS OCCLUSION

## REPORT OF A CASE

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Ligation of a main artery of the lower extremity, such as the common iliac, external iliac or common femoral, may result in gangrene even in the presence of a normal arterial system. A number of methods are available to prevent such a catastrophe from occurring. Therapeutic venous occlusion, produced by ligation of the concomitant vein when it is necessary to ligate a major artery, is one of the methods which has been advocated. This method was propounded by Makins,<sup>1</sup> a British surgeon during World War I. He collected a series of cases to show that this procedure reduced the incidence of gangrene when it was necessary to ligate a major artery to a limb. Numerous attempts in the laboratory have been made to explain this somewhat paradoxical phenomenon. Some investigators<sup>2</sup> have produced experimental evidence to prove that the actual arterial inflow to an extremity is increased after this procedure, while others<sup>3</sup> have presented evidence that it is decreased. One of the most recent articles on the subject was published by my coworkers and me.<sup>4</sup> We showed that an actual increase in the arterial inflow to a dog's hind extremity occurred after occlusion of the iliac vein both with the arterial system intact and when the femoral artery had been occluded (figs. 1 and 2). The Rein thermostromuhr method of measuring blood flow,<sup>5</sup> which measures cubic centimeters of blood per minute flowing through a given blood vessel, was used. It was also demonstrated that the actual increase in arterial blood flow took place during the period of venous occlusion and not after the release of it. Collens and Wilensky<sup>6</sup> in 1936 reported the use of a pneumatic tourniquet to produce

From the Surgical Service of the Massachusetts General Hospital.

1. Makins, G. H.: (a) Hunterian Oration, 1917, on the Influence Exerted by the Military Experience of John Hunter on Himself and on the Military Surgeons of Today, *Lancet* **1**:249, 1917; (b) *Gunshot Injuries to the Blood-Vessels*, New York, William Wood & Company, 1919.

2. Holman, E.: (a) *Surgery of Large Arteries*, *Ann. Surg.* **85**:173, 1927. (b) Holman, E., and Edwards, M. E.: A New Principle in the Surgery of the Large Arteries, *J. A. M. A.* **88**:909 (March 19) 1927. Pearse, H. E.: A New Explanation of the Improved Results Following Ligation of Both Artery and Vein, *Ann. Surg.* **86**:850, 1927. Theis, F. V.: Ligation of Artery and Concomitant Vein in Operations on Large Blood Vessels, *Arch. Surg.* **17**:244 (Aug.) 1928.

3. Brooks, B., and Martin, K. H.: Simultaneous Ligation of Vein and Artery, *J. A. M. A.* **80**:1678 (June 9) 1923. Brooks, B.: Surgical Applications of Therapeutic Venous Obstruction, *Arch. Surg.* **19**:1 (July) 1929. Montgomery, M. L.: Therapeutic Venous Occlusion, *ibid.* **24**:1016 (June) 1932.

4. Linton, R. R.; Morrison, P. J.; Ulfelder, H., and Libby, A. L.: Therapeutic Venous Occlusion, *Am. Heart J.* **21**:721, 1941.

5. Rein, H.: Die Thermostromuhr. Ein Verfahren zur fortlaufenden Messung der mittleren absoluten Durchflussmengen in uneröffniten Gefassen in situ, *Ztschr. f. Biol.* **87**:394, 1928. Herrick, J. F., and Baldes, E. J.: Thermostromuhr Method of Measuring Blood Flow, *Physics* **1**:407, 1931.

6. Collens, W. S., and Wilensky, N. D.: (a) Intermittent Venous Occlusion in Treatment of Peripheral Vascular Disease, *J. A. M. A.* **109**:2125 (Dec. 25) 1937; (b) The Use of Intermittent Venous Compression in Treatment of Peripheral Vascular Disease, *Am. Heart J.* **11**:705, 1936.

intermittent venous occlusion in the treatment of chronic obliterative arterial disease. A pressure in the tourniquet at or slightly below diastolic blood pressure was recommended. The effect of this method of venous occlusion on the arterial inflow to a dog's extremity was studied also with the Rein thermostromuhr, and an increase was observed during the period of occlusion similar to that produced by venous ligation (fig. 3).

The purpose of this paper is to present a case in which acute arterial occlusion of the ipsilateral external iliac and hypogastric arteries in a woman aged 58 years was treated with intermittent venous occlusion. Gangrene of the extremity was prevented despite the absence of all arterial pulsations in the leg. The patient was discharged from the hospital three weeks after the arterial occlusion, at which

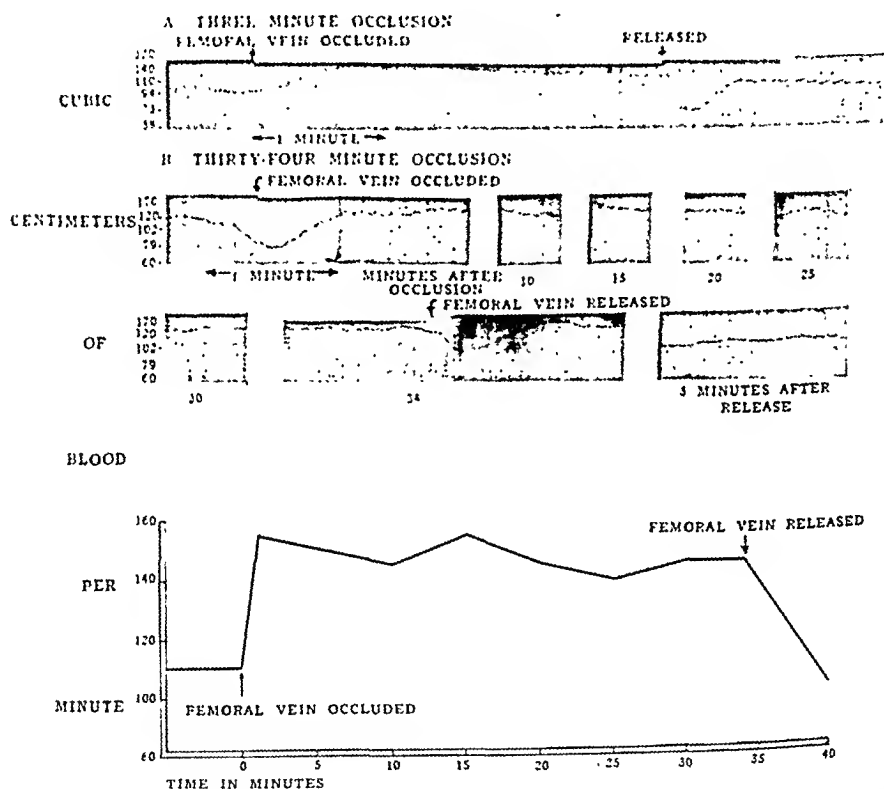


Fig. 1.—The effect of venous occlusion in the ipsilateral limb on the normal arterial blood flow to an extremity (sodium amytal anesthesia). Note the rapid increase in the flow of blood in the femoral artery after occlusion of the femoral vein in the three minute occlusion record, namely from 100 cc. per minute to 230 cc. per minute. In the thirty-four minute record, the increase is from 110 cc. per minute to 155 cc. per minute. It is also to be noted that the blood flow persisted at 145 cc. per minute until the femoral vein was released. This shows that the increase in arterial blood flow is concomitant with the venous occlusion. Figures 1, 2 and 3 have been previously published (Linton and others<sup>4</sup>).

time she was able to walk about the hospital. Two years and three months later, at the time of this report, she was able to walk without discomfort.

#### REPORT OF CASE

A 58 year old white native American woman was first admitted to the Baker Memorial Hospital Jan. 29, 1940 with a five months' history of slowly increasing abdominal distention, weakness and loss of weight. Associated with these symptoms she had had frequent attacks of crampy abdominal pain and some intermittent severe pain in the left costophrenic angle. The menopause had occurred in 1932, but in the eight or nine months preceding admission

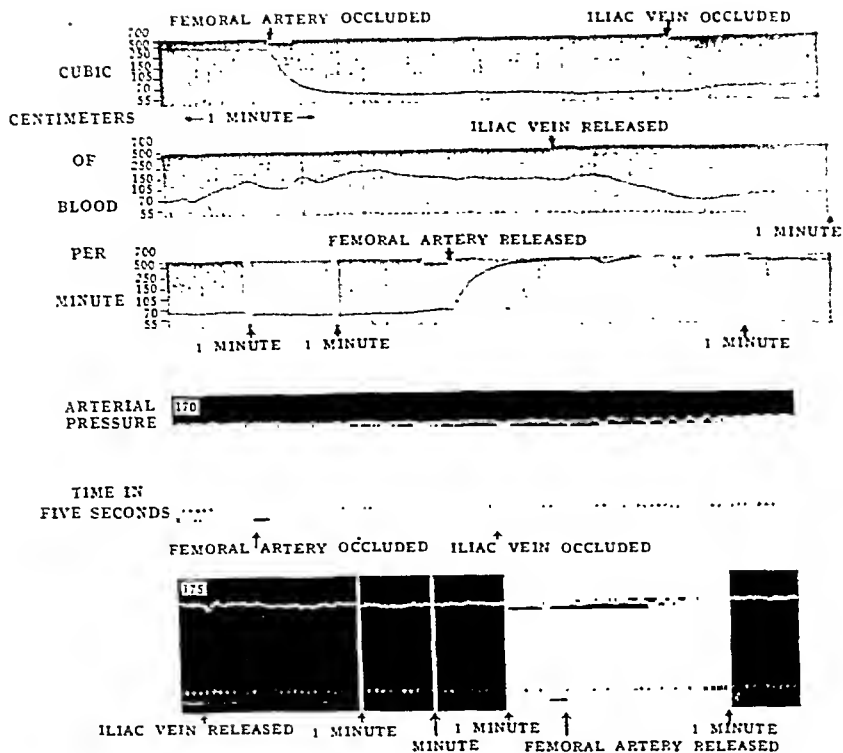


Fig. 2.—The effect of venous occlusion on the flow of blood in the iliac artery in the presence of acute arterial insufficiency (sodium amylt anesthesia). After occlusion of the femoral artery, note the decrease in arterial blood flow from 450 cc. a minute to 60 cc. a minute, and the increase in blood flow to 140 or 150 cc. a minute after occlusion of the iliac vein. It will be seen that this increase persisted as long as the occlusion was present and that after the release of the iliac vein the flow returned to the preocclusion level. This experiment had no effect on the blood pressure of the animal.

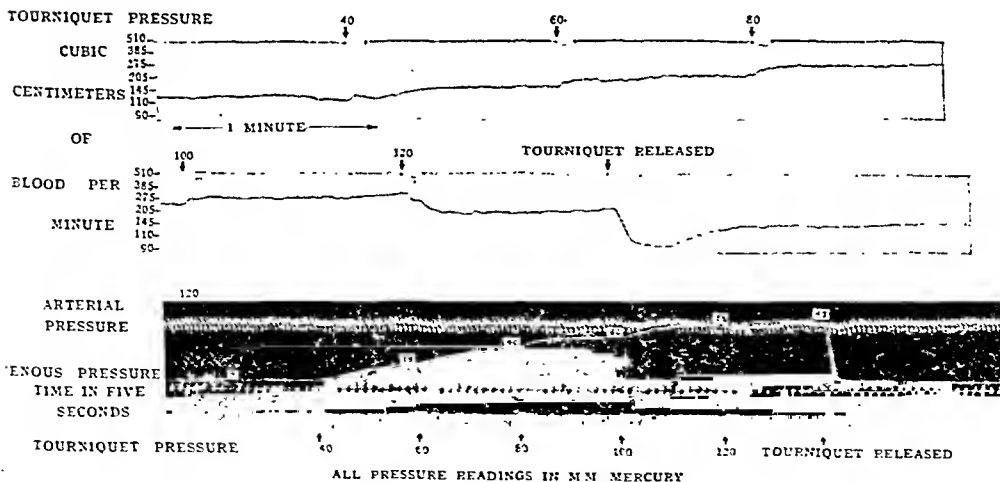


Fig. 3.—The effect on the flow of blood in the iliac artery of increasing venous pressures by means of a pneumatic tourniquet applied to the thigh. It is to be noted in this record that with each increase in the venous pressure of the extremity by raising the pressure in the tourniquet there was an increase in the arterial blood flow until the venous pressure reached a level above 75 mm. of mercury. It will be seen that the venous pressure can be elevated much higher by this means than by ligation of the main vein of an extremity. The blood flow was increased by this means from 115 cc. a minute to 280 cc. a minute, whereas obstruction of the iliac vein in the same animal produced a rise from 115 cc. a minute to only 215 cc. a minute.



to the hospital she had had a slight amount of vaginal bleeding at intervals. In the last month severe orthopnea and dyspnea had developed. She required many pillows in order to sleep at night. She had been married thirty-six years and had two daughters who were living and well.

Physical examination revealed an emaciated elderly woman sitting in a chair. When she lay down she became extremely dyspneic. The heart beat was irregular, with numerous extrasystoles, and the apex beat was palpable well out in the axillary line. The blood pressure was 156 systolic and 82 diastolic. There was complete flatness throughout the right side of the chest with a shift of the mediastinum to the left. Abdominal examination revealed a hard, irregular mass filling the lower part of the abdomen and extending above the umbilicus. It appeared fixed at the brim of the pelvis. Sounds due to peristalsis were unusually loud, but there did not seem to be any significant degree of intestinal distention. There was a small amount of free fluid in the abdomen. Pelvic examination showed the uterus to be small. The pelvic examination indicated that the mass arose in the region of the left ovary with some infiltration of the broad ligament. A note was made at this time that because of the possibility of infiltration it was thought that the tumor might be inoperable. Examination of the lower extremities revealed pitting edema of both ankles. There was good pulsation in the dorsalis pedis and the posterior tibial artery of both feet. A diagnosis of carcinoma of the left ovary, right-sided hydrothorax and extrasystoles of the heart was made. A roentgen examination of the chest confirmed the diagnosis of hydrothorax. On January 30, 2,700 cc. of reddish wine-colored fluid was removed from the right pleural cavity. Microscopic examination of this fluid revealed that it contained 35,700 red blood cells and 16,800 white blood cells per cubic millimeter and 16.7 Gm. of hemoglobin per hundred cubic centimeters. The differential blood smear showed 76 per cent polymorphonuclear cells, 12 small lymphocytes, 8 monocytes and 4 eosinophils. The red blood cells appeared normal, and the platelets were slightly increased. A roentgenogram of the chest after the removal of the fluid revealed a round, thick mass in the central pulmonary field opposite the eighth rib posteriorly, and there were also a number of smaller masses at the base of the left lung behind the heart shadow and a large sharply defined mass in the lower mediastinum.

In view of these findings it was considered that the patient had metastatic disease involving the lungs, farther advanced on the right side. Accordingly she was given a series of roentgen treatments and was discharged from the hospital on March 3. She refused operation at this time because she was greatly improved so far as her general condition and dyspnea were concerned.

She was readmitted to the hospital on April 10, in much the same condition in which she had been discharged except that the fluid in the right side of the chest had reaccumulated. The blood pressure was 185 systolic and 95 diastolic. A thoracentesis was performed and yielded 2,880 cc. of straw-colored fluid. The red cell count was 560 and the white cell count 6 per cubic millimeter of fluid. A laparotomy was performed on April 16 and a large solid carcinoma of the left ovary, measuring 23 cm. in diameter, was removed. The removal of the tumor was difficult because it was closely adherent to the left side of the pelvis. The left ureter passed through the mass, so that it was necessary to sacrifice it and remove the kidney. Damage to the hypogastric artery during the removal of the tumor made ligation necessary. The sigmoid loop of the colon was closely adherent to the growth and had to be dissected from it, and it was necessary to sacrifice the superior hemorrhoidal artery because it was involved in the tumor mass.

At the time of the operation it was thought that the left external iliac artery had not been damaged, but later developments proved this not to be the case. It probably was not ligated but was so severely traumatized that it became thrombosed. The patient was seen within two hours after the operation, at which time she was fairly well oriented and complained that her left foot was numb and cold and that she could not move it. Examination at this time revealed that the left leg was absolutely pulseless; even a femoral pulsation in the groin could not be made out. The blood pressure was 140 systolic and 80 diastolic. Intermittent venous occlusion was immediately commenced, a pneumatic tourniquet being placed as high on the thigh as possible. This was inflated to 50 mm. of mercury and left for nine minutes. At the end of this time the toes assumed a definite pink color. The pneumatic tourniquet was then released for one minute, and the leg immediately blanched. Intermittent venous occlusion was continued for the next forty-eight hours without interruption, with a cycle of nine minutes on and one minute off. During this period there was a gradual improvement in the circulation of the extremity, so that at the end of forty-eight hours it was possible to change the cycle to four minutes on and two minutes off. On April 26, the tenth postoperative day, intermittent venous occlusion was omitted all night because the patient was complaining of pressure on the thigh from the tourniquet and because considerable

edema of the left ankle had developed. The following morning the foot was warm, dry and pink. Subsequently the intermittent venous occlusion was used two hours on and one hour off during the day, with a cycle of three minutes on and three minutes off. On April 30, fourteen days after the operation, treatment was discontinued. The abdominal wound healed per primam intentionem. The patient was allowed out of bed on the fifteenth postoperative day and was discharged on May 3, the seventeenth postoperative day, at which time she was walking about the hospital.

Since her discharge from the hospital she has been examined a number of times. Her chief complaint has been of pain in the back. Roentgen examination revealed a destructive process involving the bodies of the thoracic portion of the spine. This lesion responded well to roentgen therapy, and on July 16, 1942 her condition had greatly improved. Her left leg still has no pulsations in it, and there are only slight oscillations in the thigh. When she has been standing all day there is a tendency toward edema, but this is controlled well with

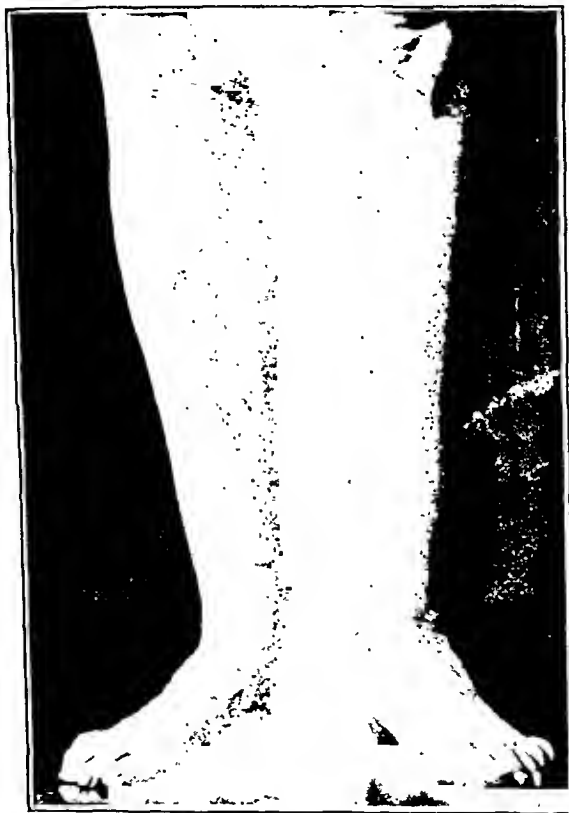


Fig. 4.—A photograph of the patient's legs taken two years and three months after occlusion of the left external iliac artery and the hypogastric artery. Note that the left leg is normal in appearance compared with the right one except for slight swelling. There is no evidence that any of the toes had been gangrenous. No pulsations or oscillations were demonstrable at this time. Nevertheless the patient was able to walk a considerable distance without pain.

an elastic stocking (fig. 4). She is able to walk a distance of about a mile without pain, although not without some fatigue.

#### COMMENT

This case is of interest because it shows the value of the proper use of intermittent venous occlusion in the treatment of a case of acute major arterial occlusion. There can be little question that the arterial circulation to this patient's leg was seriously impaired. It is believed that without treatment gangrene of the foot and lower part of the leg would have developed.

Examination of the arterial system (fig. 5) indicates how meager the collateral arterial supply to the extremity was in this case. Blood could get to the extremity only via the direct anastomoses between the femoral artery and the epigastric and the deep circumflex iliac artery and indirectly through the branches of the hypogastric artery via the anastomoses with the ovarian, uterine, pubic and pudendal arteries of the same and the opposite side of the body. Nevertheless it was possible by means of intermittent venous occlusion to preserve the extremity and give the patient a useful leg.

It should be pointed out that ligation of the hypogastric artery and occlusion of the external iliac artery constitute a more serious arterial lesion than ligation

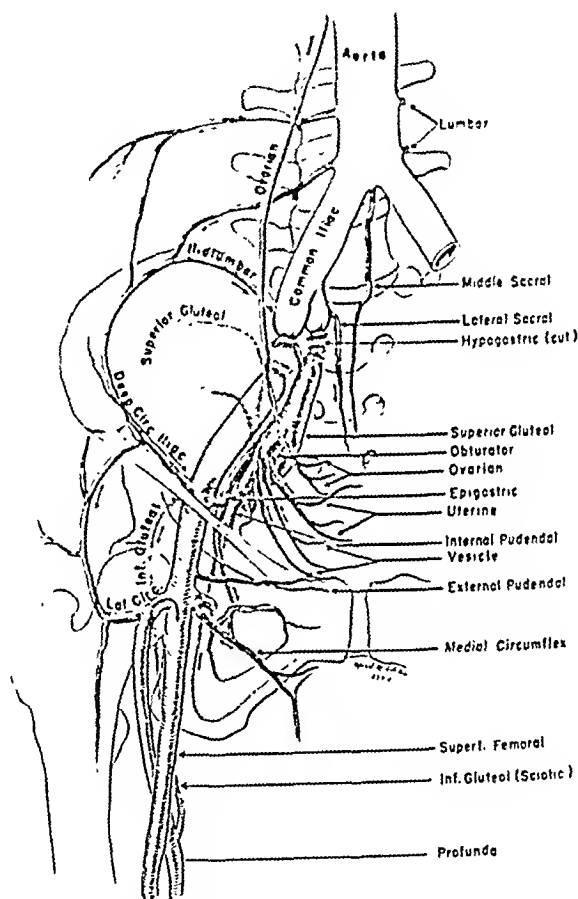


Fig. 5.—An anatomic drawing showing the collateral arterial circulation to the leg after division of the external iliac and the hypogastric artery. This lesion is comparable to the one described in this article. The chief collateral blood supply to the leg after such a vascular occlusion is from the lumbar arteries and epigastric arteries of the same side. The blood from the former reaches the femoral artery through anastomosis with the deep circumflex iliac artery, while the latter connects directly with it. A small amount of blood also reaches the extremity indirectly through obturator and inferior gluteal arteries, branches of the hypogastric artery from anastomoses of the ovarian, uterine, internal pudendal, external pudendal and medial circumflex arteries with the corresponding arteries of the opposite side of the body. It is obvious that the amount of blood reaching the leg through these channels must be greatly reduced from the normal, yet in spite of this it was possible with intermittent venous occlusion to prevent gangrene and save the extremity.

of the common iliac artery above its bifurcation (fig. 6). The reason is that when the common iliac artery is ligated any arterial blood entering the hypogastric artery through its collateral channels will be able to reach the extremity through the

external iliac artery, which of course is impossible if both arteries are occluded, as occurred in this case. Further evidence to substantiate this view is the statement made by Halsted<sup>7</sup>: "Ligation of the common iliac (artery) less endangers the vitality of the lower extremity, and makes easier the establishment of collateral circulation than does ligation of the peripheral vessels, for example, the external iliac (artery)."

The surgical removal of the large tumor was undertaken only with the patient's realization that her condition was critical and also that removal might not be possible. The surgical procedure that was carried out is perhaps open to some criticism, chiefly because of the lack of full realization of the damage to the external

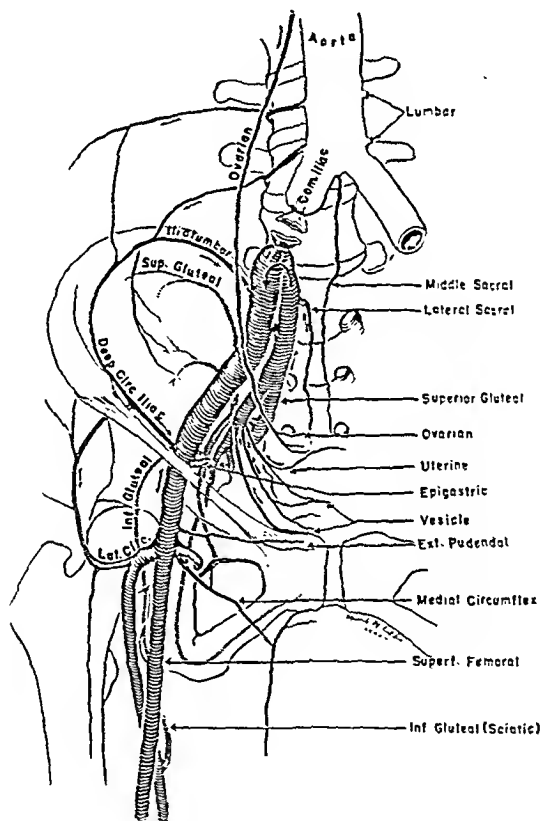


Fig. 6.—An anatomic drawing showing the collateral arterial circulation to the leg after division of the common iliac artery. Note that the blood which enters the hypogastric artery through its collateral channels can readily pass distally through the external iliac artery. Division of the common iliac artery, therefore, will not endanger the vitality of the extremity to the same extent as the lesion shown in figure 5.

iliac artery and the failure to ligate the common iliac vein. Furthermore, if a similar situation should arise again the importance of removing the lumbar ganglions on the left side would be recognized. Under the circumstances in this case removal could readily have been accomplished, since the ganglions were almost completely exposed when nephrectomy was done. These omissions are recognized, and the purpose in presenting the case is to show the value of intermittent venous occlusion in what seemed almost to be a hopeless situation.

7. Halsted, W. S.: The Effect of Ligation of the Common Iliac Artery on the Circulation and Function of the Lower Extremity, *Bull. Johns Hopkins Hosp.* 23:191, 1912.

The technic of intermittent venous occlusion used in this case needs emphasis. The pneumatic tourniquet was applied as high as possible on the thigh, and the leg was elevated to the level of the heart, so that during the period of release of the venous occlusion the blood would readily empty from the veins of the leg. The pressure in the pneumatic tourniquet was maintained at 50 mm. of mercury. The cycle used for the first forty-eight hours was nine minutes of occlusion followed by one minute of release. The long period of occlusion in relation to the short period of release is considered highly important in the proper use of the intermittent venous occlusion. Thus in this case after inflating the tourniquet it was possible to see the gradual return of color to the extremity from above downward. Nine minutes was required for it to reach the ends of the toes, and as soon as the pressure in the venous tourniquet was released the leg, foot and toes blanched quickly. These observations corroborate the laboratory observations that it is during the period of venous occlusion that the arterial blood flow is augmented and that after release of pressure the flow decreases. As the collateral circulation gradually improved it was possible to change the cycle to one of four minutes of occlusion with two minutes of release.

Success in the treatment of major arterial occlusion by this method depends on several factors. First, and most important, the treatment should be commenced as soon as possible after the occurrence of the arterial occlusion. In the case reported intermittent venous occlusion was begun within two hours. If a period of eight hours or longer is allowed to elapse, intravascular thrombosis may occur in the distal part of the extremity and will preclude any chance to save the limb. Second, the extremity should be placed at the level of the heart, so that when the pressure in the tourniquet is released the blood and lymph will drain from the limb. The use of shock position if necessary for the general treatment of the patient is no contraindication to the use of intermittent venous occlusion, but allowance must be made in the timing of the cycle, since with the patient in this position blood will enter the extremity more slowly and drain out of it with greater rapidity. If it is necessary to keep the head much higher than the extremities, for instance in a patient with cardiac disease, intermittent venous occlusion should not be used, because the resulting venous and lymphatic stasis will produce edema and interference with the capillary circulation. Third, the pneumatic tourniquet should be placed as far proximal on the extremity as possible in order to include as much as possible of the collateral circulation. In the case reported it was placed on the thigh just distal to the groin. Fourth, a pressure of 40 to 50 mm. of mercury in the pneumatic tourniquet has been found to be the most effective, providing the systolic blood pressure is above 100 mm. of mercury. If the patient's blood pressure is below this level a lower pressure should be used in the tourniquet, so that there is a difference of at least 50 mm. of mercury between the systolic blood pressure and the pressure in the tourniquet. Fifth, the cycle should be determined for each case and checked each day the treatment is continued. The tourniquet is inflated with the extremity at the same level as the heart, or in the position it will be necessary to maintain during the treatment. The appearance of the extremity will be waxen at first, but gradually a pinkish color will be seen to creep distalward until it reaches the tip of the digits. The time in minutes required for change in color after inflation of the tourniquet should represent the "on" part of the cycle. In cases in which the change in color may not be so apparent, the time required for the superficial veins of the distal part of the extremity to become engorged should be taken. In the case reported nine minutes was the "on" period determined when treatment was commenced. Subsequently it was reduced to four

minutes as the circulation improved. It is unusual to have such a long period, but this is explicable since the arterial occlusion had been so high and practically complete. If the occlusion is more distal a four to six minute period of occlusion is more desirable. A period shorter than four minutes seldom if ever is to be recommended.

The "off" period is likewise determined by deflating the tourniquet. This should be the time in minutes required for the distal part of the extremity to blanch or the superficial veins to empty of blood. In the case reported a one minute "off" period was used when the treatment was commenced. Later this was increased to two minutes, to correspond with the improvement in the circulation and also to permit the disappearance of the edema which had formed as a result of the long (nine minute) "on" period and the short (one minute) "off" period.

In cases of severe arterial occlusion, such as the case reported, continuous treatment both day and night is recommended until the circulation improves sufficiently to permit rest periods of one to two hours between periods of three to four hours of treatment. In the case reported it was necessary to use an ordinary sphygmomanometer for the tourniquet, since the automatic type of electrically

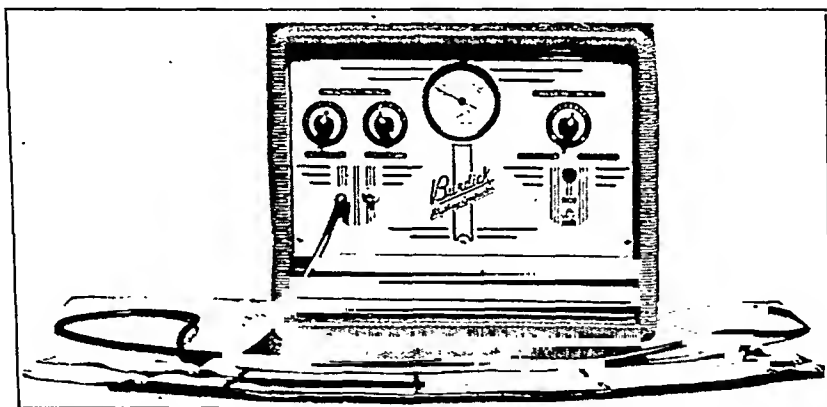


Fig. 7.—A photograph of the Burdick intermittent venous occlusion apparatus. This machine has separate controls which permit "on" periods of one to ten minutes and "off" periods of one to six minutes. By this means any type of cycle can be obtained.

controlled machines did not permit a nine minute "on" and a one minute "off" cycle. The cuff of the sphygmomanometer was inflated and deflated manually every ten minutes for the first forty-eight hours by the patient's nurses. As the result of experience with this patient it is now possible to get any cycle with an "on" period of one to ten minutes and an "off" period of one to six minutes with the Burdick automatic electrical machine for producing intermittent venous congestion (fig. 7).

In a woman 58 years of age the arterial blood supply to the left leg was interrupted by ligation of the hypogastric artery and occlusion of the external iliac artery secondary to trauma. Adequate arterial circulation was reestablished in the leg and gangrene was prevented by means of intermittent venous occlusion, a long period of occlusion and a short period of release being used. The technic of intermittent venous occlusion for the treatment of acute arterial occlusion is discussed.

# DEMEROL.

## A SUBSTITUTE FOR MORPHINE IN THE TREATMENT OF POSTOPERATIVE PAIN

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AND

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It is the purpose of this paper to present in greater detail a report of the effectiveness of demerol, a new synthetic analgesic, for the control of postoperative pain and restlessness. A complete discussion<sup>1</sup> of the properties of the drug, including its effectiveness, safety and potency in the treatment of a large variety of conditions, has already been presented by one of us (R. C. B.).

Demerol<sup>2</sup> (1-methyl-4-phenyl-piperidine-4-carboxylic acid ethyl ester hydrochloride) was introduced by Eisleb and Schaumann<sup>3</sup> in 1939 and was almost immediately acclaimed by numerous investigators<sup>4</sup> as a potent and safe analgesic approaching morphine in effectiveness. Its advantages, especially its antispasmodic properties, soon became apparent. Thus the atropine-like effect combined with sedative action makes it an ideal drug for the treatment of severe colicky pain. With exception of rare hypersensitive persons, demerol may be used without contraindication in patients with severe anemia, disease of the liver or kidneys or bronchial asthma. Of particular importance is the rarity of occurrence of respiratory depression in patients treated with demerol. This has been noted only three times: once in a group of 1,119 medical and surgical patients<sup>1</sup> and twice in a group of 338 patients receiving the drug for preanesthesia.<sup>5</sup> In each case it occurred in a person over the age of 60 who presented advanced debilitation and cerebral arteriosclerosis. Other advantages and minor disadvantages will be considered in the discussion of the results.

From the Departments of Therapeutics and Surgery, New York University College of Medicine, and the Third Surgical Division (New York University), Bellevue Hospital.

1. Batterman, R. C.: Clinical Effectiveness and Safety of a New Synthetic Analgesic Drug. *Dermol, Arch. Int. Med.* **71**:345 (March) 1943; abstracted, *Federation Proc.* **1**:143, 1942.
2. The Alba Pharmaceutical Company, Inc., New York, has supplied us with the drug and other aid in connection with this investigation. Demerol was introduced in Europe as "eudol" and was subsequently known on that continent and in South America as "dolantin."
3. Eisleb, O., and Schaumann, O.: Dolantin, ein neuartiges Spasmolytikum und Analgetikum (Chemisches und Pharmakologisches), *Deutsche med. Wchnschr.* **65**:967 (June 16) 1939.
4. (a) Dolle, W.: Dolantin, ein neues Spasmolyticum und Analgeticum in der Gynäkologie, *Prakt. Arzt* **25**:113, 1940. (b) Rosenthal, H.: Beobachtungen zur Bekämpfung des Wundschmerzes mit dem neuen Analgetikum, Dolantin, München, *med. Wchnschr.* **86**:1079 (July 14) 1939. (c) Schäfer, F.: Schmerzbekämpfung in der Chirurgie mit Dolantin, *Deutsche med. Wchnschr.* **65**:970 (June 16) 1939. (d) Schlungbaum, H.: Schmerzbekämpfung mit Dolantin, einem synthetisch hergestellten Spasmolytikum und Analgetikum, *Med. Klin.* **35**:1259 (Sept. 22) 1939. (e) Sostmann, H. E.: Zur Ablösung des Morphins und seiner Abkömmlinge in der Gynäkologie durch Dolantin, *Med. Welt* **14**:325 (March 30) 1940. (f) Althoff, H.: Klinische Erfahrungen mit Dolantin-Bayer, *Therap. d. Gegenw.* **6**:258, 1939. (g) Dietrich, H.: Klinische Erfahrungen mit einem neuen synthetischen Spasmolytikum und Analgetikum, *Deutsche med. Wchnschr.* **65**:969 (June 16) 1939. (h) Klein, E. K.: Erfahrungen mit Dolantin; einem myotrop und neurotrop wirkenden Spasmolytikum, München, *med. Wchnschr.* **86**:1674 (Nov. 24) 1939. (i) Reisinger, F.: Das neue Analgetikum und Spasmolytikum Dolantin, *Wien. med. Wchnschr.* **90**:400 (May 25) 1940. (j) Heydner, W.: Erfahrungen mit dem Spasmo-Analgetikum Dolantin bei Herzkranken, *Fortschr. d. Therap.* **16**:33 (Jan.) 1940.
5. Rovenstine, E. A., and Batterman, R. C.: The Utility of Demerol as a Substitute for the Opiates in Preanesthetic Medication, *Anesthesiology*, to be published.

## SCOPE OF INVESTIGATION

The cases of 488 postoperative patients, 165 of whom had had abdominal section, are available for analysis. There was no criterion for the selection of patients other than that they be conscious and cooperative at the time of admission to the surgical ward. The majority of the postoperative patients had received demerol for preanesthesia. The results of this use of the drug are included in another report.<sup>5</sup>

Demerol was dispensed in tablets of 50 mg. each for oral use (research number D-140) and in solution (research number S-140) in ampule or vial so that 1 cc. contained 50 mg. The dose varied between 50 and 150 mg., orally or parenterally, in a single dose or in repeated doses several times daily. In the final analysis the dose and the route of administration were taken into consideration. The same patient may at different times have received varying doses by different routes. A variation may have occurred but once, or repeatedly, over an extended period. The effectiveness of a certain dose, given either orally or parenterally, was considered as an individual trial and recorded as such. For example, 41 patients were subjected to appendectomy. All received demerol parenterally, and 4 were treated in addition with the oral preparation. Among those treated by injection varying doses were tried with 5, so that a total of 46 trials became available for analysis in this group.

## CONTROL OF POSTOPERATIVE PAIN

The effectiveness of demerol immediately becomes apparent when its ability to control postoperative pain is observed. Among the 164 patients receiving the drug parenterally during the postoperative period after laparotomy (table 1) 95.5 per cent of the 182 trials resulted in complete, satisfactory relief of the pain, discomfort and restlessness. After procedures other than laparotomy demerol is only slightly less effective (table 2). Thus in 91.5 per cent of 271 trials in 252 cases, postoperative pain was completely controlled. An additional 5.2 per cent experienced a moderate effect, or relief for approximately three hours.

The after-effects of rectal operations are notoriously painful, occasionally necessitating the use of large doses of opiates. In this group there was failure to give a satisfactory response to demerol in only 4 instances out of 45 trials, and even in the 4 patients who failed to respond in one trial the subsequent administration of a larger dose resulted in alleviation of the pain.

Regardless of the severity of the condition, the duration of the operation, the age of the patient and the ultimate prognosis, with rare exceptions the administration of 75 to 100 mg. of demerol parenterally every three to four hours, if necessary, was sufficient to make the patient comfortable and facilitate the usual therapeutic procedures. Many patients were in the period of effect of the anesthetic agent, which probably influenced the results to some extent. However, postoperative control of pain was hitherto achieved only by the use of morphine or one of its derivatives.

Orally, demerol was effective when the pain was not severe or after the acute postoperative symptoms had subsided. Satisfactory control of the pain was achieved in approximately 87 per cent of 123 trials on 118 patients (table 3). It is thus possible to continue using and to rely on the oral preparation if the postoperative discomfort should persist for several days.

In the postoperative phase of treatment demerol was found to be a safe drug, rarely causing untoward reactions. The subjective responses of dizziness and nausea, which in two other series<sup>1</sup> were noted in approximately 20 and 8 per cent of the patients respectively, occurred rarely in this particular study. Here again the anesthetic may have influenced the incidence of untoward reactions. The incidence of vomiting was no higher than one would expect after major operations. Comment regarding the rarity of respiratory depression has already been made. Since demerol has been in use in the surgical service there has been no instance of respiratory depression in a postoperative patient. Here obviously is a distinct advantage over the opiates, for respiratory depression resulting from frequent and repeated use of



TABLE 1.—Effectiveness of Demerol (Parenterally) for Control of Pain and Restlessness Following Laparotomy

Type of Operation	Number of Patients	Number of Trials	Effectiveness *												
			Complete: Dose, Mg.			Moderate: Dose, Mg.			Slight: Dose, Mg.			None: Dose, Mg.			
			50	75	100	50	75	100	50	75	100	50	75	100	
Appendectomy.....	41	46	3	23	19	1	..	..	..	..	..	..	..	..	..
Exploratory operation.....	32	35	1	8	23	1	..	2	..	..	..	..	..	..	..
Gastrostomy.....	10	12	2	4	6	..	..	..	..	..	..	..	..	..	..
Jejunostomy.....	2	2	1	1	..	..	..	..	..	..	..	..	..	..	..
Gastric resection.....	15	15	..	4	10	..	..	1	..	..	..	..	..	..	..
Repair of perforated peptic ulcer.....	6	7	..	1	6	..	..	..	..	..	..	..	..	..	..
Gastroenterostomy.....	6	6	..	..	6	..	..	..	..	..	..	..	..	..	..
Cholecystectomy.....	10	18	1	5	12	..	..	..	..	..	..	..	..	..	..
Cholecystostomy.....	6	6	..	3	3	..	..	..	..	..	..	..	..	..	..
Choledeobgastrostomy.....	1	1	..	..	1	..	..	..	..	..	..	..	..	..	..
Release of intestinal obstruction.....	7	10	1	2	6	..	..	..	..	..	..	..	..	..	..
Colonic resection.....	8	9	1	4	4	..	..	..	..	1	..	..	..	..	..
Colostomy.....	14	15	..	4	11	..	..	..	..	..	..	..	..	..	..
Total.....	164	182	10	59	106	2	..	3	..	9	..	..	..	..	..
Per cent †.....			95.5			2.6			1.1			..			..

\* Different doses may have been used in the same case.  
† In terms of number of trials (182) regardless of dose administered.

TABLE 2.—*Effectiveness of Demerol (Parenterally) for Control of Pain and Restlessness Following Operations Other Than Laparotomy*

Type of Operation	Number of Patients	Number of Trials	Effectiveness *															
			Complete: Dose, Mg.				Moderate: Dose, Mg.				Slight: Dose, Mg.				None: Dose, Mg.			
			50	75	100	150	50	75	100	150	50	75	100	150	50	75	100	150
Inguinal herniorrhaphy.....	41	46	2	13	30	..	..	1	..	..	..	..	..	..	..	..	..	
Femoral herniorrhaphy.....	4	5	1	1	3	..	..	..	..	..	..	..	..	..	..	..	..	
Ventral herniorrhaphy.....	8	8	..	2	0	..	..	..	..	..	..	..	..	..	..	..	..	
Thyroidectomy.....	12	12	..	1	11	..	..	..	..	..	..	..	..	..	..	..	..	
Radical mastectomy.....	7	10	..	3	7	..	..	..	..	..	..	..	..	..	..	..	..	
Radical mastectomy.....	5	6	..	2	4	..	..	..	..	..	..	..	..	..	..	..	..	
Sacrospinal resection.....	0	0	..	2	7	..	..	..	..	..	..	..	..	..	..	..	..	
Amputation, toes.....	7	8	..	2	5	..	..	..	..	..	1	..	..	..	..	..	..	
Amputation, mid thigh.....	2	2	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..	
Amputation, others.....	3	4	..	2	2	..	..	..	..	..	..	2	..	..	..	..	..	
Thoracotomy.....	41	45	1	4	31	..	1	2	2	..	..	1	..	2	..	..	..	
Hemorrhoidectomy.....	20	22	..	4	10	..	..	..	1	..	..	..	..	..	..	..	..	
Miscellaneous rectal operations.....	8	8	..	3	4	..	..	..	1	..	..	..	..	..	..	..	..	
Excision of pilonidal sinus.....	27	27	1	9	14	..	..	2	..	..	..	1	..	..	..	..	..	
Incision and drainage.....	11	12	..	2	7	..	1	..	2	..	..	..	..	..	..	..	..	
Open reduction of fracture.....	2	2	..	..	2	..	..	..	..	..	..	..	..	..	..	..	..	
Illo graft.....	5	6	..	1	3	..	..	..	..	..	..	..	..	1	..	1	..	
Skin graft.....	20	27	..	8	17	1	1	..	..	..	..	..	..	..	..	..	..	
Incision, miscellaneous.....	9	9	..	1	8	..	..	..	..	..	..	..	..	..	..	..	..	
Ligation of saphenous vein.....	2	3	..	1	2	..	..	..	..	..	..	..	..	..	..	..	..	
Miscellaneous procedures.....	253	271	5	62	180	1	3	5	0	..	1	4	..	1	2	1	..	
Totals.....			91.6				6.2				1.8				1.4			
Per cent {.....																		

\* Different doses may have been used in the same case.

† In terms of number of trials (271) regardless of dose administered.

TABLE 3.—Effectiveness of Demerol (Orally) for Control of Pain and Restlessness Following Operations Other than Laparotomy

Type of Operation	Number of Patients	Number of Trials	Effectiveness •											
			Complete: Dose, Mg.			Moderate: Dose, Mg.			Slight: Dose, Mg.			None: Dose, Mg.		
			50	75	100	150	30	75	100	150	30	75	100	150
Inguinal herniorrhaphy.....	13	13	3	1	7	..	..	..	..	..	..	..	..	..
Femoral herniorrhaphy.....	1	1	..	..	1	..	..	..	..	..	..	..	..	..
Ventral herniorrhaphy.....	2	2	..	..	2	..	..	..	..	..	..	..	..	..
Thyroidectomy.....	1	1	..	..	..	..	..	..	..	..	..	..	..	..
Radical mastectomy.....	2	2	..	..	2	..	..	..	..	..	..	..	..	..
Sacroperineal resection.....	2	2	..	..	1	..	..	..	..	..	..	..	..	..
Amputation, toes.....	5	5	..	..	5	..	..	..	..	..	..	..	..	..
Amputation, mid thigh.....	3	3	..	..	2	1	..	..	..	..	..	..	..	..
Hemorrhoidectomy.....	14	15	1	1	8	..	..	..	..	..	..	..	..	..
Miscellaneous rectal operations.....	0	7	..	..	5	..	..	..	..	..	..	..	..	1
Excision of pilonidal sinus.....	4	4	..	..	3	..	..	..	..	..	..	..	..	..
Incision and drainage.....	22	22	3	1	16	..	..	..	..	..	..	..	..	..
Open reduction of fracture.....	6	8	3	1	4	..	..	..	..	..	..	..	..	..
Bone graft.....	1	1	1	..	..	..	..	..	..	..	..	..	..	..
Skin graft.....	3	3	1	..	2	..	..	..	..	..	..	..	..	..
Incision, miscellaneous.....	23	24	6	1	14	..	1	..	..	..	..	..	..	..
Ligation of saphenous vein.....	7	7	2	..	5	..	..	..	..	..	..	..	..	..
Miscellaneous procedures.....	3	3	1	..	2	..	..	..	..	..	..	..	..	..
Total.....	118	123	21	6	70	1	1	1	11	..	..	2	..	1
Per cent †.....			86.9			10.5			2.4					

• Different doses may have been used in the same case.  
† In terms of number of trials (123) regardless of dose administered.

morphine is a cause for grave concern. With several patients who had received morphine (during the transition period of our study) and in whom respiratory depression had developed, it was possible to continue the administration of demerol for the control of pain without producing this serious side effect.

Of postoperative complications, urinary retention may be most troublesome. Catheterization, especially if repeated at frequent intervals, may result in cystitis or pyelonephritis. The incidence of catheterization among consecutive postoperative patients receiving morphine in one male surgical ward was determined for a period of ten months. During this period 160 operations were performed; 20 patients, an incidence of 12.5 per cent, required catheterization within twenty-four to forty-eight hours postoperatively. In the same ward in the following eleven months, in which demerol was used exclusively, there were 178 consecutive postoperative patients, of whom 14, or 7.8 per cent, required catheterization. There is no doubt that the type of surgical procedure plays a significant role in the development of urinary retention and must be considered in an evaluation of the results just cited. The majority of the patients who were catheterized, whether they received morphine or demerol, had had a rectal operation, a herniorrhaphy or an operation on the lower part of the abdomen. Although the number of postoperative patients is too small and the difference in incidence of urinary retention between patients given morphine and those given demerol may not be statistically significant, it is our belief, nevertheless, that demerol is less likely to produce this undesirable complication. Furthermore, in a group of 812 nonoperative and medical patients urinary retention was noted only once and was not particularly detrimental to the patient's welfare.

In regard to abdominal distention and pulmonary complications we have no data. However, in many patients "gas" pains were effectively relieved. The antispasmodic action of demerol and the lack of constipation may be definite advantages. The drug has little if any action on the cough reflex and hence does not encourage accumulation of bronchial secretions. The dryness of the mucous secretions attributable to its atropine-like action and the bronchial dilatation that it produces are also advantages. The latter is of particular help to patients with bronchial asthma, for whom morphine is contraindicated.

The only disadvantage of demerol as far as postoperative use is concerned is its short action. This, however, is rarely apparent in the first postoperative day. For patients with a protracted and "stormy" course the average dose may be sufficient for only two hours. This may be overcome either by administering the same dose more frequently or by increasing the dose. There is no particular danger of causing undue depression in such cases.

#### COMMENT

It is our conclusion following these observations on a group of postoperative surgical patients that demerol is a more suitable drug for the control of pain than morphine or any of its derivatives. It has the distinct advantage of rarely producing respiratory depression. Other preferable qualities are its antispasmodic effect on gastrointestinal tract and bronchi, its atropine-like drying action on mucous membrane and its lack of suppression of the cough reflex. It has the relatively unimportant disadvantage of short action, which may be overcome by frequent dosage. The occasional symptoms of dizziness and nausea which have followed administration in other trials were not encountered in this series. These experiences indicate that demerol as a substitute for morphine is equally effective, and safer, for postoperative patients.

Miss Aniele C. Evaskitis, research nurse of the Department of Therapeutics, New York University College of Medicine, assisted in the preparation of this paper.

# MISCONCEPTION ABOUT THE "SPRINGINESS" OF THE LONGITUDINAL ARCH OF THE FOOT

## MECHANICS OF THE ARCH OF THE FOOT

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From the earliest days of anatomic knowledge the longitudinal arching of the foot has been looked on as designed to provide resilience and has been compared in its shape and function to a spring. This view is expounded in the classic textbooks of anatomy, and has been retained by more contemporary writers, as the term "spring ligament" implies.

The twenty-seventh English edition of Gray's "Anatomy" states:

The chief characteristic of this [medial longitudinal] arch is its resilience, due to its height and to the number of joints between its component parts. . . . It should be observed that in a normal foot the arches become flattened when erect posture is assumed and are restored when the weight of the body is taken off the feet. This resilience accounts for the suppleness of the normal foot and enhances the value of the arches by rendering possible such rapid and sudden movements as running and jumping.<sup>1</sup>

In the seventh edition of Cunningham's "Textbook of Anatomy" <sup>2</sup> it is written:

These arches do not merely support the body weight statically as arches of masonry support a bridge: the presence of the joints in the arches introduces a spring mechanism so that the arches resemble the half-elliptical springs of a carriage. They yield slightly when weight is put upon them, and recoil when it is removed. . . . The tension of the plantar calcaneo-navicular ligament, supported by the tibialis posterior muscle, resists the tendency of the weight of the body to drive the head of the talus downwards between the bones which it braces together, and the resilience it imparts to the medial arch is recognised in its common appellation—the spring ligament.

The same interpretation of the function and purpose of arches was given by the more modern authors Callander <sup>3</sup> and Grant.<sup>4</sup> The former stated:

The ligaments act only as passive agents, in contrast to the muscles which take an active part and are indispensable for the maintenance of the proper shape of the arch. Because of the elasticity of the ligamentous apparatus, the arches flatten out when the foot has to sustain a heavy weight, but they regain their original shape immediately when the weight is removed.

Grant <sup>4</sup> continuously referred to the arches of the foot as "springs." He recommended that the foot be regarded "as a spring rather than as an arch."

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Delivered in brief by invitation at the annual meeting of the American Orthopedic Association, Baltimore, June 5, 1942.

From the service of Dr. Leo Mayer, Hospital for Joint Diseases and the service of Dr. J. J. Nutt, New York Polyclinic Medical School and Hospital.

1. Gray, H.: *Anatomy: Descriptive and Applied*, ed 27, New York, Longmans, Green & Co., 1938, p. 517.

2. Cunningham, D. J.: *Textbook of Anatomy*, ed. 7, London, Oxford University Press, 1937, pp. 374 and 379.

3. Callander, C. L.: *Surgical Anatomy*, ed. 2, Philadelphia, W. B. Saunders Company, 1939, p. 802, fig. 442; p. 520, plate 23, figs. 2 and 3.

4. Grant, J. C. B.: *A Method of Anatomy: Descriptive and Deductive*, ed. 2, Baltimore, William Wood & Company, 1940, pp. 411, 412 and 454.

Figure 373 on page 412 of his book "A Method of Anatomy: Descriptive and Deductive" is intended to illustrate this and also to prove that

when you place your foot on the ground the spring will, of course, flatten under your weight. . . . At the hinge surfaces between the talus and the navicular and also between the navicular and the three cuneiforms the spring of the arch can flatten and recoil.

Thus it is evident that the arch of the foot has been generally recognized as an elastic recoiling spring from as far back as when the plantar calcaneonavicular ligament was nicknamed "spring ligament" up to the present day.

#### SPRINGINESS OF THE LONGITUDINAL ARCH OF THE FOOT

The purpose of this paper is to give a critical analysis of this concept. It will first be necessary to consider certain well known mechanical laws.

It is known that the progress of a moving body can be arrested only by application of a sufficient force, or reaction, acting in a direction opposite to that of the movement of the body. The extent of the force necessary to stop a moving body, or as it is called in mechanics the reaction force, depends on the time it takes to bring the body to rest. It is impossible to bring any moving body to rest instantly. Some time, no matter how short, must elapse between the application of the retarding force and the cessation of motion. A greater reaction force must be applied in order to stop a moving body in a shorter time. The degree of shock or resilience which a moving body experiences is controlled entirely by the length of time required to bring it to rest or to change its direction of motion. In other words, the more sudden the stop or change of the direction of motion, the greater will be the shock. Shock absorption or resilience is usually secured in machinery by devices, such as air buffers, rubber pads or steel springs, which possess elasticity—that property of a body which enables it to change its shape under action of a force on it and to resume its original shape when the action of the force is removed. A steel spring or a piece of rubber can be compressed or bent, but it will promptly return to its original form when the force is released.

As an example, consider a half-elliptic spring interposed between the axle of the wheel and the body of a wagon (fig. 1 *A*). When the wheel rides over a prominence in the road it is suddenly pushed upward. The spring flattens and at the same time becomes longer because its anterior and posterior points are separated from each other. Thus the sudden upward motion of the wheel is slowed down by the gradual flattening of the spring, and the shock, which without the spring would be completely transmitted to the body of the wagon, is diminished or absorbed by the spring.

Walking on a stilt is rather jarring, because with each step the downward motion of the body is abruptly stopped the moment the stilt comes in contact with the ground. If, however, a compressible coiled spring (fig. 1 *B*) is incorporated beneath the lower end of the stilt, the time between the contact of the spring with the ground and complete cessation of downward motion of the stilt will be increased, and resilience will be supplied. The degree of resilience depends on the extent of the vertical compressibility of the coiled spring. The longer or higher the coiled spring, the slower will be the stop, and therefore the less will be the shock.

Resilience may also be provided by a half-elliptic curved spring (fig. 1 *C*) attached to the lower end of the stilt. The shock-absorbing action of such a device will depend on the height (*h*) of the curve. It is obvious, therefore, that the shock-absorbing function of the curved spring is entirely measured by its ability to

flatten. In its turn the flattening of the spring cannot occur unless its ends ( $S, S$ ) are freely movable against the ground and are able to spread apart in position  $S', S'$ , when the curve of the spring flattens approaching a straight line.

A somewhat similar shock absorber may be built at the end of the stilt by substituting for an elastic curved spring two pieces made of some comparatively nonelastic rigid material, such as wood or bone, which are hinged to each other in an archlike fashion and connected at their two free ends by some elastic material, such as a tension coiled spring (fig. 1 *D*).

A more complicated shock absorber, built somewhat on the pattern of the human foot, is presented in figure 1 *E*. Several rigid pieces corresponding to the skeleton of the foot are hinged together and connected to each other by coiled springs which correspond to the plantar ligaments and plantar fascia.

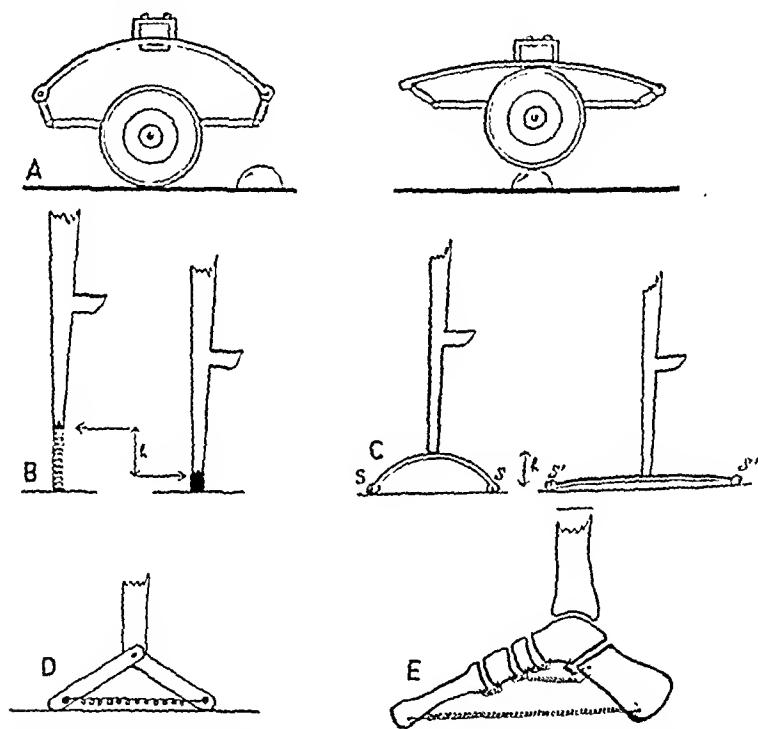


Fig. 1.—*A*, effect of a semielliptic spring interposed between the axle of a wheel and the body of a wagon. *B*, effect of a coil spring attached to the lower end of a stilt. *C*, effect of a half-elliptic spring. *D*, a shock absorber with two rigid arms whose free ends are joined by a coil spring. *E*, a shock absorber made up of several rigid pieces corresponding to the skeleton of the human foot and joined by coil springs.

All that was said in reference to the half-elliptic spring holds true in the case of the rigid wooden shock absorber. The higher its arch, the more resilience it will provide. In addition, two requirements must be fulfilled: First, free mobility must be present in the joints between the separate rigid links of the arch (at least at the joint at its apex); second, each of the ends of the links or at least their two free ends must be connected by some elastic material. Without these neither flattening nor recoiling of the arch would be possible; in other words, the whole device would lose its springiness and become rigid.

Thus, in order that the human foot may possess springiness, it is necessary that the plantar fascia and the plantar ligaments be elastic, or capable of stretching when the weight of the body is borne on the foot and resuming their original length in the non-weight-bearing foot.

According to Gratz,<sup>5</sup> "certain fibrous tissues were found to withstand stress up to a maximum of 1,476 Kg. per square centimeter (20,959 pounds per square inch)" of cross section. Their tensile strength was found to be approximately equal to that of soft steel wire of the same weight. The elasticity of human ligamentous, fascial and other fibrous structures, in the sense of their ability to return to their original shape, was given as more than 500 Kg. per square centimeter (7,100 pounds per square inch), although the elasticity of many tissues exceeded this point. However, the elongation of these structures was negligible, amounting to less than 2 per cent, with tensile load of 100 Kg. per square centimeter of cross section.

The plantar fascia in man is approximately 15 cm. long and has a cross section of at least 0.5 sq. cm. According to precise calculations by Mr. Emilio Pittarelli, an engineer with whom I consulted, the estimated tensile load of plantar fascia is roughly 35 Kg. in a man with average body weight of 60 Kg., standing on one foot in a relaxed position. Consequently, the maximum elongation of the plantar fascia cannot be more than 1.4 per cent of its length.<sup>6</sup> Under such conditions, the plantar fascia may elongate from its original length of 15 cm. to approximately 15.21 cm. This in its turn will allow for sagging of the apex of the longitudinal arch (head of the talus) amounting close to 0.1 cm.

It seems reasonable to assume that the shock-absorbing property of the human foot is only of theoretic interest and of no practical value if "flattening and recoiling" of the arch can take place only within the range of about 0.1 cm. It is evident, then, that the foot is a rigid structure and cannot be compared, as it has been erroneously until now, to a "semielliptic spring."

#### CONSTRUCTION AND PURPOSE OF THE LONGITUDINAL ARCH

If the longitudinal arch does not provide springiness, what then are its mechanical construction and its purpose?

Man is the only primate who possesses a longitudinal arch; he is likewise the only primate in whom the foot has been perfected for use as a lever in upright bipedal terrestrial progression. It is the writer's belief that the longitudinal arch of the foot was developed in response to functional requirements for increased strength of the foot as a lever.<sup>7</sup>

In designing any structure engineers select materials for the different parts according to the resistance to the particular stresses each part of the structure is expected to bear.<sup>8</sup> In a suspension bridge, as a rule, steel beams are used for the parts under compression stress and cables in places of tensile stress. In the human foot the skeletal parts which possess a great resistance to compression stress and are comparatively weak in tension are analogous to the beams, while the liga-

5. Gratz, C. M.: *Biomechanical Studies of Fibrous Tissues Applied to Fascial Surgery*, Arch. Surg. 34:461-495 (March) 1937; *Tensile Strength and Elasticity Test of Human Fascia Lata*, J. Bone & Joint Surg. 13:334-340, 1931.

6. It is estimated that if the elongation is 2 per cent with a load of 100 Kg. per 1 sq. cm. of cross section, it will be 4 per cent with a load of 100 Kg. per 0.5 sq. cm. of cross section, and roughly 1.4 per cent with a load of 35 Kg. per 0.5 sq. cm. of cross section.

7. The muscular action will be disregarded for the time being, as for example in the case of a foot with complete paralysis of all the muscles.

8. Stress in mechanics is defined as the result of that part of the force which does not produce motion. If a rubber band is stretched to double its size, part of the force produces motion and the rest (stress) helps to keep the ends of the rubber band apart. Mechanics recognizes tensile stress, which tends to separate particles of material, compression stress, which tends to bring them closer together, and bending stress, which is really a combination of the other two.



mentous tissue, which is able to withstand great tensile stress, is analogous to the cables. It is a well known fact that the bone ruptures first under tension, causing cortical avulsion fracture, while severing of the ligaments is rather uncommon.

If the foot consisted of one solid piece of bone without ligaments it would be subjected to bending stress. In other words, its dorsal bone trabeculae would be subjected to compression and its plantar trabeculae to tension in a manner somewhat similar to the distribution of stresses in a simple beam (fig. 2 *A*). Since the solid bony foot has a comparatively weak tensile strength, it cannot stand much bending and would tend to break.

It is also obvious that no suspension bridge could be built with very elastic cables. Likewise, the ligamentous structures of the foot (such as the plantar fascia, the plantar calcaneonavicular ligament and all the other ligaments of the foot) can withstand a tremendous tensile stress, if the force is applied in the direction parallel to their fibers, without showing any appreciable increase of their length; in other words, their elongation is negligible.

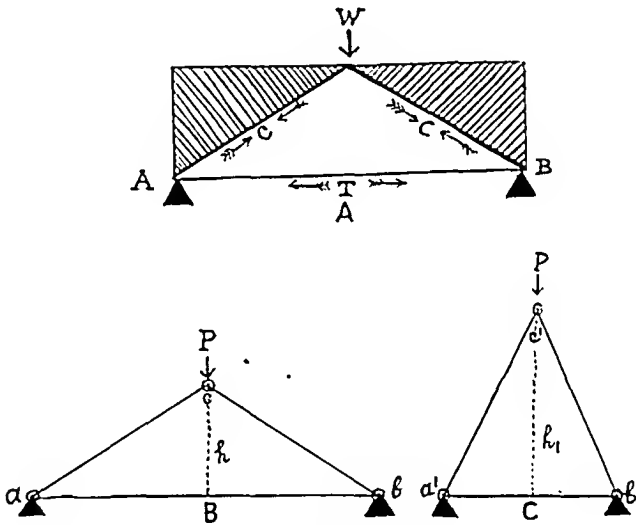


Fig. 2.—*A*, cross section illustrating distribution of stresses in a simple beam. *B*, a simple roof truss. *C*, effect of decreasing the length of a truss. The load on all the members of a truss is inversely proportionate to its height. With the same load, *P*, the compression stress over the struts (*a'c'* and *b'c'*) of truss *C*, and also the tensile stress on its tie rod (*a'b'*) is less than the stresses experienced by the corresponding members of truss *B*, because *h*<sub>1</sub> is greater than *h*. Therefore, truss *C* is a stronger structure than truss *B* and can withstand a much greater load. Truss *C* is shorter than truss *A* (*a'b'* is smaller than *ab*); consequently, the reaction at the points *a'* and *b'*, being inversely proportionate to the length of the truss, is greater than that over the corresponding points, *a* and *b*.

Engineers build so-called trussed structures in order to avoid bending stresses. A simple beam (*AB*, fig. 2 *A*) supported at both ends and loaded in the middle is subjected to bending stress. Its bottom (solid line *T*) is under tension; the upper part, under compression. The compression forces run diagonally along the solid lines *C, C*. The two cross-hatched wedge-shaped portions over the upper part of the beam do not participate in bearing any load. These parts are useless and can be removed for the sake of economy of material and in order to decrease the weight of the whole structure. Thus a simple beam and, likewise, a solid osseous foot are really identical in effect with a truss (figs. 2 *B* and *C*).

Merriman<sup>9</sup> gave the following definition of a truss:

a jointed structure which is arranged to carry loads in such a manner that each principal member is subjected to stress only in the direction of its length, that is to a tensile or compressive stress, and bending stress is eliminated. . . . In order that a truss may perfectly conform to the above definition it is necessary that the loads should be supported only at the joints, for flexural stresses will result if they are placed at other points on the members. It is further important, in order to secure rigidity, that the elementary figures included between the truss members should be triangles, since a triangle cannot change its shape without altering the lengths of its sides. A rectangular or polygonal figure, on the other hand, may change its shape without altering the lengths of its sides, and hence may be lacking rigidity.

The simple roof truss (fig. 2 B) consists of two struts ( $ac$  and  $cb$ ) which are subjected only to compressive stress running along their length. The tensile stress is entirely taken up by the tie rod ( $ab$ ) connecting the two free ends ( $a$  and  $b$ ) of the struts, preventing them from spreading apart.

According to mechanics, the load on all the members of the truss (compressive on the struts and tensile on the tie rod) is inversely proportionate to its height ( $h$ ). The higher the truss, the less load will be borne by its members; consequently, the same truss with an increase of its height will be able to withstand a greater load. In other words, the strength of the truss increases proportionately to its height.

Likewise, the reaction at each end ( $a$  and  $b$ ) of the truss is inversely proportionate to its length ( $ab$ ). In other words, if the length of the truss decreases, the load borne by its ends ( $a$  and  $b$ ) will increase. The decrease of the length of the truss (provided the length of its struts,  $ac$  and  $cb$ , remains the same) actually consists of a shortening of its tie rod ( $a_1b_1$ , fig. 2 C). It is evident that the truss will become higher if it is shortened ( $H_1 > h$ , fig. 2 C). Therefore, shortening of the truss, with a resultant increase in its height, will also increase the load (reaction) at its end.

If these theoretic considerations of a truss are applied to the "foot truss," it can be understood why a foot with a high arch is stronger than a flat foot; and at the same time why the anterior and the posterior point of support in pes cavus (especially the anterior, represented by the metatarsal heads) bear more weight than in a foot with a low arch.

#### THE HUMAN FOOT AS A TRUSSED STRUCTURE<sup>10</sup>

The human foot (fig. 3) may be considered to be built as a trussed structure, in which the skeletal parts form struts which are subjected to compression stresses and the plantar fascia acts as a tie rod taking up all the tensile stresses. In this way

9. Merriman, M.: A Text-Book on Roofs and Bridges: Stresses in Simple Trusses, New York, John Wiley & Son, 1914, p. 1.

10. For the sake of simplicity the human foot has been considered as a simple trussed structure. However, according to the analysis of Mr. E. Pittarelli, it would be more appropriate to classify the foot as a rigid frame with a horizontal tie rod. The principal stresses, when the weight of the body is borne, are tension in the tie rod (plantar fascia) and mainly compression in the rigid frame (foot skeleton). However, the compression stresses in the rigid frame (foot skeleton) are distributed on its dorsal side, its plantar side being subjected to tension. This tension is resisted by the plantar ligaments which bind the bones together. That is why the plantar ligaments of the foot are much more powerfully developed than the dorsal ones. If the plantar ligaments were omitted, the rigid frame formed by the foot skeleton would collapse. If the tie rod (plantar fascia) were omitted, the condition of rigid frame without tie rod would develop; then the plantar ligaments would have to take up the entire tensile stress (also that which is normally borne by the plantar fascia). Under such circumstances the load on the plantar ligaments would be too great, and they would be overtaxed.



in that it became more rigid and hence served as a stronger lever. This was a necessary evolutionary step in response to the new functional requirement in connection with adaptation to the upright plantigrade terrestrial stride.

#### ROLE OF LIGAMENTS AND MUSCLES IN MAINTENANCE OF LONGITUDINAL ARCH

Although it is not within the scope of this paper to go into a detailed discussion of the function of the muscles of the foot, some consideration must be given to their part in maintaining the integrity of the longitudinal arch.

Steindler<sup>11</sup> stated on one page in his book that "the integrity of the form of the foot is entrusted first to its ligamentous and secondly to its muscular apparatus." Nevertheless, five pages later he wrote: "In maintenance of the normal configuration of the foot the muscles stand in first line of defense; the ligamentous resistances are invoked against external forces only after muscular resistance has failed. In other words, the question of equilibrium is, first of all, a problem of muscle tension."

The prevailing opinion as to the dependence of the longitudinal arch upon muscle support was voiced by Sir Arthur Keith,<sup>12</sup> who stated: "The arch of the human foot is safeguarded and maintained by the reflex postural action of muscles, ligaments being merely second line defenses. Flat foot results from a defect in this defense."

Probably the reverse is true. The integrity of the longitudinal arch in the usual standing position depends mainly on the passive tensile strength of the ligaments binding the bones together and on the plantar fascia's acting as a tie rod in the foot truss. The muscles are used to assist the ligamentous structures in locomotion and when the latter are overloaded, as during the lifting of a heavy weight.

In a normal relaxed standing position the muscular action most probably is limited to maintaining a balance between the leg and the foot. A mere muscular tonus may be adequate enough for this purpose. The muscles come into play only in order to keep the weight-bearing line of the body in plumb line so that balance may be maintained by the force of gravity itself, with the least possible expenditure of energy.

The following considerations are advanced in favor of the importance of the ligamentous structures rather than the muscles for maintaining the arch:

1. The height of the longitudinal arch in the weight-bearing foot does not decrease in a fully anesthetized person or in a cadaver with no active muscular function present, and yet the passive support of the ligamentous structure is still available.

2. Flattening of the longitudinal arch would be a logical expectation in cases of complete paralysis of the muscles of the leg and foot if the muscles were more important than the ligaments in support of the arch. However, in many cases of anterior poliomyelitis observed by me in which weight was borne on a foot completely deprived of muscular support and with only the ligaments intact, no appreciable flattening of the longitudinal arch, as compared with that of the opposite unaffected foot, was noted after observation for many years. As a matter of fact, it has been not infrequently observed that the affected foot may sometimes show

11. Steindler, A.: *Mechanics of Normal and Pathological Locomotion in Man*, Springfield, Ill., Charles C Thomas, Publisher, 1935, pp. 261 and 266.

12. Keith, A.: *The History of the Human Foot and Its Bearing on Orthopedic Practice*, J. Bone & Joint Surg. **11**:10-32, 1929.

exaggeration of the longitudinal arch (cavus deformity). This may occur in cases in which a trace of power is left in the short plantar muscles, which, being unopposed by the plantar flexors and the dorsiflexors, bring the calcaneal tuber and the metatarsal heads closer together. As a result of this the plantar ligamentous structures become shortened before the patient becomes ambulatory, leading to permanent cavus deformity.

3. Normal standing for more than a few minutes would be impossible because of muscular fatigue if the longitudinal arch were mainly supported by muscular effort. Then usual plantigrade standing would be just as exhausting as standing on the tips of the toes.

4. Nature's design in biomechanical construction always conforms with the rules of economy in material and energy. It is hardly conceivable that such a waste of muscular energy would be permitted.

In the seventh edition of Cunningham's "Textbook of Anatomy," R. D. Lockhart<sup>13</sup> shows lateral roentgenograms of the foot taken in a standing position with muscles contracted and with muscles relaxed as fully as possible. These roentgenograms demonstrate that the longitudinal arch is slightly higher during muscular contraction and that the foot flattens when the muscles are relaxed. Tracings of the roentgenograms prove quite conclusively that simultaneously with the decrease of the height of the longitudinal arch in the state of relaxation, the anterior point of the foot (metatarsal heads) is somewhat more distant from the heel; in other words, the foot shortens on contracture of the muscles and elongates when they are relaxed. Engels,<sup>14</sup> after taking accurate roentgenograms of feet with and without weight bearing, also concluded that the longitudinal arch is slightly higher without weight bearing and becomes lowered when the weight of the body is put on the foot. These observations cannot be looked on as proof that the muscles are the "first line of defense" (Keith<sup>12</sup>) or "indispensable" (Callander<sup>3</sup>) in maintaining the longitudinal arch. If anything, it demonstrates the opposite, namely, that the muscles are subject to fatigue and give way after a short time. Thus the integrity of the longitudinal arch in prolonged standing must necessarily depend primarily on the passive resistance of the ligamentous apparatus.

These considerations likewise do not seem to substantiate the statement of Sir Arthur Keith<sup>12</sup> "that the flat-foot results from a defect in this defense [muscular defense]."

It is true that in walking the muscles come into greater play, because they not only are called on to maintain balance but in addition must lift and propel the whole weight of the body. Since different muscular groups act alternatively, there is a short interval between the muscular contractions allowing rest and restoration of muscular energy. However, even in walking there is a tendency to utilize the passive resistance on the foot truss and the force of gravity, with muscular assistance being employed only when the load becomes excessive.

The intrinsic short plantar muscles, because of their small size and development, need little consideration. They were originally planned to move the toes. They should be looked on as a remnant from the days of prehensile function of the foot, when the toes played a more important role. In the modern human foot the short plantar muscles and, likewise, the toes themselves (except the hallux) show an evolutionary tendency toward retrogressive development; this is especially true of the fifth toe.

13. Lockhart, R. D., in Cunningham,<sup>2</sup> p. 516, fig. 438.

14. Engels, W.: Ueber normalen Fuss und der Plattfuss, Deutsche Ztschr. f. orthop. Chir. 12:461-503, 1904.

## SHOCK-ABSORBING MECHANISM OF THE FOOT

While the "springiness of the arch" must be looked on as highly improbable, there is a definite shock-absorbing function of the foot in locomotion. This is manifested by a certain mechanical arrangement at the talocrural articulation.<sup>15</sup>

There is a phase in walking when one leg is advanced forward with the foot in dorsiflexion (fig. 4 *A*). The body is allowed to fall forward until the heel of the advanced foot comes in contact with the ground. This downward progression of the whole leg column with the superimposed body weight is suddenly stopped by the ground, and shock is produced. The shock can be diminished by increasing the time between the initial contact of the heel with the ground and the complete cessation of the downward progression of the body. This is accomplished by the retarding action of the dorsiflexor muscles of the foot.

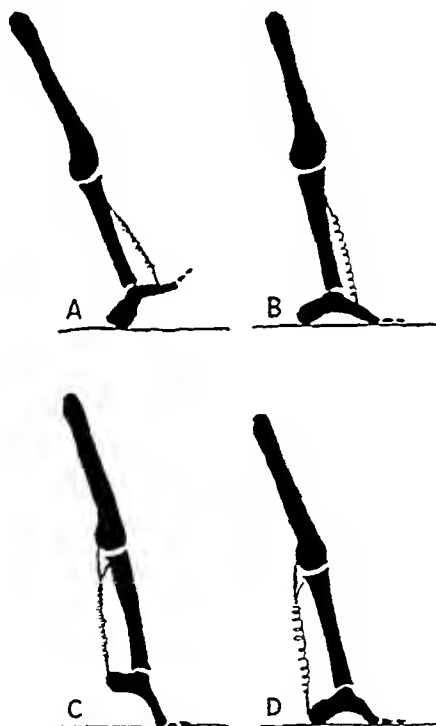


Fig. 4.—Phases in walking. *A*, one leg is advanced with the foot in dorsiflexion. *B*, relaxation of the anterior tibial muscle permits the sole to be placed flat on the ground. *C* and *D*, analogous function of the triceps surae muscle during "toe first" gait or "goose stepping."

For simplicity's sake, let the anterior tibial muscle be considered as representing all of the dorsiflexor muscles of the foot. As the heel touches the ground the anterior tibial muscle is gradually allowed to relax from its original state of full contraction. Thus the ankle is slowly brought down until the entire sole of the foot comes in contact with the ground. In this action the anterior tibial muscle may be compared to a tension coiled spring incorporated between the leg and the foot (fig. 4 *A*). It is clear that this mechanism supplies resilience by increasing the time between the beginning of retardation of motion and the complete stop. The total length of the leg column is originally increased by the length of the heel

15. Mr. John Pinaud, a mechanical engineer, must be credited for the clarification of this mechanical phenomenon and some other points concerning the mechanics of the foot.

bone, since the latter becomes almost vertical in complete dorsiflexion of the foot (fig. 4 *A*). As the foot is slowly lowered, the total length of the leg column gradually diminishes up to the point when the entire sole rests on the ground and the heel resumes its horizontal position (fig. 4 *B*). The jarring "steppage gait" of the patient with paralyzed dorsiflexor muscles of the foot (drop foot) can be easily understood as resulting from lack of retarding action of these muscles. The same holds true after Pirogoff's amputation, when there is no ankle joint to absorb the shock.

A somewhat similar condition is present during "toe first" gait or "goose stepping." In this instance the triceps surae muscle supplies the retarding action instead of the anterior tibial muscle (figs. 4 *C* and *D*).

The triceps surae muscle also plays an important role in retarding the downward progress of the body during jumping from a height. It is well known that landing on the toes at the end of a jump is less jarring than landing flat on the entire sole or on the heel. Landing on the sole or the heel is the most common cause of fracture of the calcaneum, which sometimes is also associated with a fracture of the vertebral bodies. Landing on the toes provides more resilience than landing on the heel, because the toes, or rather the metatarsal heads, are farther from the axis of the ankle joint than the calcaneal tuber. Consequently, the ankle joint is in a much higher position when the toes first touch the ground with the foot in equinus than when the foot is in calcaneus and the tuber calcanei is the first to come in contact with the ground. As a result of this the retarding time is greater when the jumper lands in equinus. Besides, the much more powerful plantar flexor muscles, as compared with the dorsiflexor muscles, are better able to supply retarding springlike action when the landing is made in the equinus position.

In addition to the shock-absorbing mechanism of the ankle joint, a great part of the resilience during the act of jumping is provided by the knee and hip joints. The latter are gradually allowed to go into flexion, the time between the beginning of retardation and a complete stop thus being increased. That is why jumpers are taught to end a jump in a squatting position.

#### IDIOPATHIC FLAT FOOT

To the best of my knowledge no one has as yet proved or even demonstrated satisfactorily any muscular "defect" or abnormality in the case of idiopathic "flat foot." It has been my progressively strengthening conviction that the idiopathic "flat foot" is a congenital and often hereditary deformity. It must be looked on as an arrest of the ontogenetic development of the foot. In other words, the "flat foot" of an adult has failed to reach the stage of maturity corresponding to the person's age. One of the main characteristics (among many others which cannot be discussed here) of the adult "flat foot" (before the onset of the secondary pathologic changes) is an extreme hypermobility due to ligamentous laxity. Marked ligamentous laxity is also present in the foot of the human embryo and during the first postnatal years. Likewise, the foot of the other primates close to man exhibits even more pronounced hypermobility of the joints of the foot with ligamentous laxity. Thus the idiopathic "flat foot" is usually present at birth and decreases with age. In my opinion the possibility of the acquisition of this deformity or the flattening of the longitudinal arch with age in cases of idiopathic "flat foot" is doubtful. Traumatic, paralytic and inflammatory "flat foot," of course, are excluded from this rule, since they may develop in a normal foot.

## SUMMARY AND CONCLUSIONS

1. The human foot is a rigid lever, possessing no "springiness" (of any practical value), as is commonly believed.

2. The ligamentous structures of the foot have a definite elasticity in the sense that they are able to stretch and to resume their original length. However, the amount of elongation of the ligaments when put on stretch is insignificant, and therefore for practical purposes they can be considered as nonyielding structures. This makes improbable the generally accepted concept of the ability of the longitudinal arch to flatten under load and recoil after weight is removed. Consequently, the similarity of the longitudinal arch to "the half-elliptical spring of a carriage" must be incorrect.

3. The formation of the longitudinal arch, which is an exclusive property of the human foot and is not present in any other primates, must be looked on as a tendency to strengthen the human foot as a lever in response to functional requirements in connection with upright bipedal terrestrial progression.

4. The longitudinal "arch" of the human foot cannot be considered as a real masonry arch. The apparent arching of the foot is just one of the results of the foot's being built as a trussed structure. By virtue of the trussed construction of the foot, the bones are called on to bear mostly the compression stresses and the ligamentous structures the tensile stresses, bending stresses being completely eliminated in a truss. Such a distribution of stresses is mechanically sound, since the bones have a great resistance to compression, the ligaments to tension. The trussed construction of the human foot contributes greatly to its strength and economy of material.

5. The ligaments are mainly responsible for the integrity of the longitudinal arch. They bind together the bones of the foot in a trussed structure, the plantar fascia acting as a tie rod of the truss.

6. In normal relaxed standing the muscles form a second line of defense in support of the longitudinal arch (or a foot truss). They simply maintain the balance between the leg and the foot by keeping the weight bearing line in the plumb line. They assist the ligaments when the latter are overloaded, as in standing with a heavy load, and of course are active during locomotion.

7. Idiopathic "flat foot" is most probably a congenital and often a hereditary malformation due to arrest of the ontogenetic development and not to faulty muscular function.

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# REVIEW OF UROLOGIC SURGERY

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## KIDNEY

*Anomaly.*—Gutierrez<sup>1</sup> drew attention to the clinical indications for division of the renal isthmus in cases in which the diagnosis of horseshoe kidney has been made urographically. First are those in which there are no symptoms and in which the condition is discovered accidentally at operation; in these no surgical treatment is called for. Second are those in which horseshoe kidney is associated with urologic conditions, consisting of urinary symptoms of various kinds, with indefinite abdominal or lumbar pain and with reflex gastrointestinal disturbances, all chronic or recurring in acute attacks. These are the cases in which division of the renal isthmus is indicated for restoration of normal anatomic relationships, relief of pressure on important vessels and nerves and restoration of proper renal drainage. They constitute the great majority of clinical cases. Third are cases in which some kind of gross associated pathologic process is present in half the fused organ, for which heminephrectomy is indicated. Fourth are cases in which gross pathologic conditions are present in both halves of the fused organ, so that some kind of conservative operation, based on the degree of functional activity of each kidney, is called for.

The cases in the second group are those in which the kidneys can be restored to normal function by simple division of the renal isthmus followed by nephropexy on one side or, occasionally, on both sides. In this group the condition constitutes what Gutierrez has elsewhere described as "horseshoe kidney disease," since a very characteristic picture is presented. The principal indications for division of the isthmus after the diagnosis has been made are analyzed.

1. Gutierrez, R.: Operative Technic for Division of Renal Isthmus in Horseshoe Kidney, *Am. J. Surg.* 55:28-36 (Jan.) 1942.

The main points in the operative technic of division of the isthmus in horseshoe kidney are, according to Gutierrez, a transverse lumboabdominal incision, which will permit good exposure of the isthmus; an extraperitoneal approach to the kidney; mobilization of the kidney to be operated on by complete nephrolysis and ureterolysis; clamping and ligation of accessory blood vessels of the isthmus; double clamping of the isthmus before the renal parenchyma is divided; closure of raw surfaces by the placing of mattress sutures over interposed fat to prevent hemorrhage; pushing of the other kidney away from the midline to secure outward rotation; carrying out of nephropexy of the kidney operated on, with decapsulation of the upper pole and fixation also of the lower pole to the lateral lumbospinal muscles to provide a rotated position for the securing of adequate drainage; closure of the wound as in ordinary nephropexy, with or without the institution of drainage. Surgical results should be checked by cystoscopic examination and the making of bilateral retrograde pyelograms, which should be repeated two or three weeks after operation. In some cases the performance of nephropexy on the kidney of the opposite side subsequently will be indicated in the pyelograms made during reexaminations, to relieve pain and secure good drainage from that kidney. Gutierrez said that the excellent surgical results obtained demonstrate the value and feasibility of this conservative procedure.

*Ectopia.*—Laughlin<sup>2</sup> reported a case of renal dystopia (ectopia). Three additional members of the patient's immediate family (her baby, her mother and her sister) presented similar abnormalities. From the urologic standpoint, in his opinion, the case presents an example of an interesting class of renal anomaly; from the gynecologic standpoint, it presents a problem in differential diagnosis; from the obstetric standpoint it presents a possible complication for the pregnant period and a threat to parturition. Laughlin included a brief review of the literature on the etiology, incidence, anatomic and symptomatologic aspects, diagnosis and treatment of this condition.

McCrea<sup>3</sup> stated that the occurrence of congenital solitary pelvic kidney (congenital solitary pelvic renal ectopia) is rare. He said this condition was first described by Hénot in 1830. To date, only 34 previously reported cases are on record. Stevens, in a review published in 1937, estimated that ectopic kidneys were found once in 500 to 1,100 necropsies, whereas true pelvic kidneys occurred once in from 2,150 to 3,000 necropsies. Single kidney, or unilateral renal agenesis, occurs in a ratio of 1 to 700 to 1,610 necropsies, and he estimated that from 4 to 5 per cent of the single kidneys reported were true pelvic kidneys. Stevens concluded, then, that if solitary kidney occurs once in every 1,000 necropsies, solitary pelvic kidney would occur about once in every 22,000 necropsies.

Because of the anatomic position of solitary pelvic kidney, pathologic changes referable to the urinary tract reach a greater proportion relatively earlier in the life of the patient than do the usual anomalies of the kidney. In only 1 case reported has the patient been older than 47 years.

McCrea said that in Hinman's opinion complete absence of a kidney is best explained by the failure of the ureteral bud to develop, rather than by absence of the mesonephric blastoma, and early degeneration of the ureteral bud is a possible cause of complete absence of the kidney.

The high percentage of genital anomalies in the reported cases—17 anomalies in 35 cases—clearly demonstrates that an embryologic association exists between

2. Laughlin, V. C.: Renal Dystopia (Ectopia): A Report of an Interesting Case and Brief Review of the Literature, *J. Urol.* 47:632-641 (May) 1942.

3. McCrea, L. E.: Congenital Solitary Pelvic Kidney, *J. Urol.* 48:58-68 (July) 1942.

loss of some of its calcium salts, and when the muscular system is put at rest muscular atrophy occurs, with a concomitant reduction in the blood supply. Therefore, the reduced supply of blood to the muscles creates a relative hyperemia of the bone, and this hyperemia in turn promotes rarefaction. Although calcium is not excreted primarily through the kidney, the content of calcium in the urine is markedly increased during a period of decalcification of bone. In the event that the urine becomes highly concentrated, the calcium salt may reach a point of supersaturation and initiate a precipitate of inorganic calcium. A so-called mudstone is thus formed in the renal pelvis, the ureter or the bladder. If conditions are favorable, additional calcium is precipitated and the calculus increases in size until it may fill the entire renal pelvis and finally impair renal function. The mechanism of precipitation of salt from a saturated solution is effective in the production of calculi during the patient's recumbency, since most of the stones are composed of calcium phosphate. The role of infection in the precipitation of urinary salts is not a factor in this particular circumstance, according to Lich and Mansfield, since a large proportion of the renal stones which develop during recumbency of a patient are found in sterile urine.

Hematuria is the foremost symptom of urinary calculi associated with the type of recumbency under discussion. Hematuria usually is first manifest when the patient's position is radically changed. Renal colic, another manifestation of urinary stone, generally is accompanied by microscopic hematuria. However, in the presence of renal stone associated with enforced recumbency of a patient, renal colic is far less common than is hematuria.

The prevention of renal stones is, of course, the prime consideration. It has been demonstrated repeatedly that uninfected renal calculi in the recumbent patient can be dissolved by the maintenance of an acid urine. Lich and Mansfield expressed the opinion that it follows that in the absence of infection the formation of stones can be prevented. Decalcification of bone must be kept at a minimum. Decalcification can be reduced best by active movement of the parts of the patient's body not involved by the primary pathologic process, and massage of the affected parts affords protection from local hyperemia of bone and consequent decalcification of the bone.

The fluid balance of the patient must be carefully controlled, so that the urinary precipitation of salt is prevented. The patient must take at least 2,500 cc. of liquid daily and must take more if the loss of fluid is great because of such an added factor as fever, diarrhea or vomiting. The dietary regimen must be carefully planned throughout the entire course of the patient's recumbent period. Since the diet must produce an acid ash, the ingestion of proteins is of very definite importance. Meats, fish and cereals should be included in the daily diet, and vegetables and fruits should be intelligently employed, since they produce an alkaline urine. Fluids administered must be those which will yield an acid ash, for it would be sheer folly to advise an acid ash diet and then to permit the free taking of fluids which will produce an alkaline ash. Repeated urinalysis is an essential part of the medical regimen. At weekly intervals the hydrogen ion concentration of the urine should be determined, and, at intervals certainly no longer than a month, microscopic examination of the urine should be carried out, so that thereby a stone can be discovered long before it has produced subjective manifestations. At intervals not longer than forty-eight to seventy-two hours the patient must be made to change position completely. Lich and Mansfield said that unintelligent use of the urethral catheter is positively contraindicated among patients whose long recumbency is anticipated.

*Calcium Plaques.*—Vermooten<sup>9</sup> discussed the origin and development in the renal papilla of what have come to be known as "Randall's calcium plaques." He said that a change, identical with that which takes place during the origin and development of bone, occurs in the renal papilla but pointed out that this change rarely goes beyond the stage of deposition of calcium salts. This pathologic process, like the pathologic deposition of calcium elsewhere in the body, is most commonly associated with senescence and the gradually failing circulation which accompanies senescence.

Injury arising from any other cause than the one in question may be responsible for localized zones of calcification, Vermooten said, but cannot account for the generalized distribution of calcium so commonly seen in renal papillae, especially when Randall's calcium plaques are present. This deposition of calcium salts takes place in any of the collagen fibers in the renal papillae. It may thus be seen in the interstitial connective tissue, in the basement membrane of the collecting tubules or in the circular (spinning) fibers surrounding the small blood vessels and capillaries. Any of these zones of calcification, when it is situated immediately subepithelially, may ulcerate through the epithelium of the renal papilla and so form one of Randall's plaques. Injury to the lining epithelium of the collecting tubules by toxins and the like is quite incidental, Vermooten stated, and, although it may do so, does not necessarily play an important part in the formation of Randall's plaques.

*Tumor.*—Forsythe<sup>10</sup> reported a case of bilateral hypernephroma of the kidney. He said that a review of the literature revealed only 6 cases in which bilateral primary hypernephroma had been diagnosed and that in some of these cases the diagnosis seemed to him to be questionable. In Forsythe's case the patient was a 62 year old man who had complete urinary retention that had followed an episode of hematuria of several days' duration. Excretory urograms showed only fair excretion of dye on the left and no excretion on the right. Because of bleeding and elevation of the values for nonprotein nitrogen, the operation selected was suprapubic cystostomy. One week later excretory urograms were again made. A diagnosis of tumor of the right kidney was made. Removal of the right kidney was performed, after supportive therapy including the transfusion of blood had been carried out, and a kidney extensively involved by a tumor was removed. The patient died of cardiac failure forty-eight hours after the operation. Necropsy revealed that a tumor 4 by 6 cm. also had been present in the midportion of the left kidney. This tumor appeared to be a separate primary lesion.

Prince<sup>11</sup> reported a case of primary angioendothelioma of the kidney. He said that tumors of this type are very rare in the urinary tract; several have been reported as arising in the corpora cavernosa of the penis and in the testis and the ovary. In Prince's case the patient was a 51 year old man who complained of a dull ache in the left flank which he said had been present for two weeks. Ten years previously he had experienced a similar type of pain and gross hematuria. Cystoscopic examination indicated that hydronephrosis was present on the left, and nephrectomy was done. On removal of the kidney, it was found that instead of being large and hydronephrotic, as the pyelograms had suggested, it was small and firm and contained a tumor. The diagnosis was "angioendothelioma of the kidney."

9. Vermooten, V.: The Origin and Development in the Renal Papilla of Randall's Calcium Plaques, *J. Urol.* 48:27-37 (July) 1942.

10. Forsythe, W. E.: Bilateral Hypernephroma: Report of a Case, *J. Urol.* 47:784-786 (June) 1942.

11. Prince, C. L.: Primary Angio-Endothelioma of the Kidney: Report of a Case and Brief Review, *J. Urol.* 47:787-792 (June) 1942.

Castañó, de Surra Canard and Ortiz<sup>12</sup> presented a case in which the symptomatologic aspects of lithiasis had caused them to overlook a neoplasm, a more important disease, which was also present. About seven years previously the patient had felt a sharp pain in the left lumbar region, with extension to the testis on the same side, accompanied by hematuria and fever. Three years later the same clinical picture recurred. All that had been discovered at this time was stricture of the urethra for which dilation was carried out. The painful attacks with hematuria had increased in frequency and had brought the patient to the hospital for observation and treatment. He had a varied history of genitourinary disturbances involving the lower part of the tract. He had frank dysuria, which would disappear if he assumed the dorsal decubitus position during micturition.

A plain roentgenogram disclosed two dense shadows, one in the left kidney and one in the bladder, both of which appeared to be of the same nature and to be caused by calculi. Excretory urograms revealed the same shadow in the left kidney, but in these urograms it appeared to be larger and prolonged downward and outward. After cystoscopic examination and dilation, the calculus in the bladder was finally crushed and the fragments were eliminated spontaneously. On exploration of the left kidney, small serpentine angiomatoid veins of vermiform appearance, forming a plaque 7 cm. in diameter, were found under Zuckerkandl's fascia. When the kidney was freed, large and friable veins which bled freely were found to emerge from the parenchyma, and on removal of the plaque the veins of the parenchyma itself were seen to be of the same character. A diagnosis of malignant renal tumor was made, and nephrectomy was carried out. Histologic examination revealed a clear-celled epithelioma.

Castañó, de Surra Canard and Ortiz said that such association of lithiasis and a malignant process within the kidney is infrequent; they expressed the belief that the incidence varies between 5 and 20 per cent, these estimates including malignant tumors of both the pelvis and the parenchyma. Two theories are offered in explanation of the point of the union of these two entities. According to one, prolonged irritative action of the stone on the renal pelvis or on a calix is a predisposing element that can give rise to the neoplasm. According to the other, the stone is regarded as a result of the neoplasm; that is, the stone is formed by the lithogenic precipitation of tumoral detritus. Castañó, de Surra Canard and Ortiz said that they hold the former view in respect to the case they presented.

*Cysts.*—Gutierrez<sup>13</sup> presented a clinicoanatomopathologic classification of cystic conditions that may be found in the kidney or in the region near that organ, in which he emphasizes the fact that different types of large solitary cysts can be grouped according to number, size and anatomic location, as well as by type of the lesion and nature of its contents. Three main types are demonstrable urographically and anatomopathologically as follows: (1) The cyst is connected with a calix or the renal pelvis; (2) the cyst is not so connected but lies within the structure of the kidney, and (3) the cyst lies outside the structure of the kidney but within the region of the organ. Such cysts may be congenital or acquired. Their pathogenesis, however, remains uncertain, although some form of obstruction or trauma in the uriniferous tubules is believed always to play a part, in that it causes retention. The cysts appear most frequently at the age of the patient at which arteriosclerosis begins. They are frequently associated with some form of congenital renal anomaly. In most cases no symptoms appear until the cyst has

12. Castañó, E.; de Surra Canard, R., and Ortiz, A. A.: Cáncer de riñón y litiasis urinaria asociada, *Rev. argent. de urol.* 10:625-630 (Nov.-Dec.) 1941.

13. Gutierrez, R.: Large Solitary Cysts of the Kidney: Types, Differential Diagnosis and Surgical Treatment, *Arch. Surg.* 44:279-318 (Feb.) 1942.

attained a size sufficient for it to exert pressure on other abdominal organs. Then pain, dull or acute, abdominal or lumbar, is noticed. A cyst at the upper pole of the kidney may masquerade as a lesion of the liver and gallbladder. Gastrointestinal symptoms frequently dominate the picture. Since the cyst, except in rare instances, does not open into the renal pelvis or a calix, it is usual to find no symptoms referable to the kidney. This accounts for the infrequency with which the correct diagnosis was made in the past, before the use of pyelography and roentgenography became general. However, a cyst of large size may compress the urinary passages and cause symptoms within the urinary system. Hydronephrosis and pyonephrosis are not infrequent. Hematuria may appear, with no other assignable cause. On the basis of study of 10 cases, Gutierrez concluded that the condition can be diagnosed urographically, even in the absence of renal symptoms, whenever the cyst by compression has produced painful symptoms or the physical signs of a tumor mass palpable in one or the other side of the abdomen. He said that the most common roentgenographic and urographic observations are: (1) compression of the renal pelvis or one calix or more, (2) change in the position of the axis of the kidney, (3) inward displacement of the ureter, (4) displacement or rotation of the renal pelvis upward or downward, (5) visualization of the shadow of the cyst, (6) crescent shape of the renal pelvis or the calix, (7) calcification of the walls of the cyst in some cases, (8) visibility of the psoas muscle through the walls of the cyst, (9) shadow of the cyst superimposed on the shadow of the kidney and (10) visualization of the cyst furnished by pyelovenous backflow.

Experience shows, Gutierrez observed, that occasionally a malignant tumor is concealed within the walls of the cyst. This fact, illustrated in one of his own cases, justifies the insistence on open surgical exploration to verify the diagnosis and on removal of the cyst by a conservative operation when possible or by a radical procedure when necessary. When a tumor of the kidney is present the pyelogram as a rule discloses more extensive invasion of the calices and renal pelvis, since in increasing in size a tumor tends to spread outward. The pyelogram of a tumor also presents a more disorganized and bizarre appearance; it follows no such rule of uniformity as does the pyelogram of a simple cyst. In the case of a cyst, he pointed out, the shadow of the kidney itself usually is not enlarged.

In this series of 10 cases, 4 patients were operated on, with curative results. In 1 of these, the cyst was removed from the upper pole, and this procedure was followed by nephropexy on the right. In 2 of the 4 cases extraperitoneal lumbar nephrectomy was done and in the fourth case transperitoneal nephrectomy was performed. In all instances gratifying results were obtained. Of the 6 patients not operated on, the condition of 3 was improved and 3 were not followed. The youngest patient was 18 years old, and the oldest was 74. Five were women, and 5 were men. The diagnosis in 4 cases was made with the aid of intravenous urography and in 4 others with the aid of retrograde pyelograms. In the 2 remaining cases urography did not reveal the cyst and the diagnosis was made during operation for nephropexy. The cyst was situated in the upper pole of the right kidney in 2 cases, in the upper pole of the left kidney in 2, in the lower pole of the right kidney in 3 and in the lower pole of the left kidney in 3. Gutierrez said it was striking to note that in the 2 cases in which the diagnosis had not been made preoperatively the patients were women in whom the right kidney was low in position and readily palpable, and the urographic studies revealed marked pyelectasis, caliectasis and evidence of pyelonephritis and right nephroptosis. In 1 of these 2 cases the cyst was situated in the upper pole of the right kidney, and in the other case it was situated in the lower pole of the right kidney. Resection of the upper pole followed by nephropexy sufficed in the former of these cases; it resulted in

permanent cure of a patient who had undergone, without successful results, 2 abdominal operations for the same symptoms ten and twelve years previously. In the other case, because of anomalies of the blood supply, nephrectomy was necessary, and performance of it resulted in cure. In 1 case of the series the diagnosis was made by means of intravenous urography and was confirmed by puncture and aspiration of the fluid contained in the cyst. In the other 5 cases, in which the patients were not operated on, the diagnosis was definitely made urographically and was substantiated by clinical observation. Gutierrez said it appears that when there are enough urologic symptoms and when the preoperative diagnosis has been made, the ideal course is to advise open surgical exploration of the kidney and the cyst by simple lumbotomy, with a view to resection of the cyst by a conservative operation. Then, in cases in which the kidney cannot be saved, nephrectomy will still remain as a last resort.

*Tuberculosis.*—McClelland and Davis<sup>14</sup> discussed the relationship between skeletal and genitourinary tuberculosis. They made a study of 297 cases of tuberculosis of bones and joints, which led to the discovery of 66 cases of tuberculosis in the genitourinary tract. In this group of 297 cases of tuberculosis of bones and joints, other tuberculous foci were present as follows: pulmonary tuberculosis, 41 per cent of cases; multiple skeletal tuberculosis, 29 per cent of cases; genitourinary tuberculosis, 22 per cent of cases; no other tuberculous lesion, 35 per cent of cases. Of the 66 patients, 44 were males and 22 were females. The resultant ratio almost coincides with the ratio of 3 males to 2 females which was calculated for the entire group of 297 patients. Among the 66 patients who had skeletal and genitourinary tuberculosis, 27 (41 per cent) were dead after an average period of observation of five years. The general death rate in the hospital for skeletal tuberculosis, complicated and uncomplicated, was 28 per cent during the same period. Therefore, they said, genitourinary tuberculosis is such a serious complication of tuberculosis of bones and joints that it increases the death rate by nearly 50 per cent.

McClelland and Davis said there is an 18 per cent chance that genitourinary tuberculosis will develop in patients who have a single skeletal tuberculous focus. Among the patients who have multiple skeletal lesions there is a 32 per cent chance that genitourinary tuberculosis will develop. Many patients suffering from genitourinary tuberculosis have had no symptoms.

Creevy<sup>15</sup> stated that renal tuberculosis may heal under proper hygienic management and reported a case of demonstrably bilateral, minimal, destructive tuberculosis. The patient was well eleven years after the apparent onset of the disease, and ten years after the last demonstrable bacteriologic evidence of activity of the disease. Calcium had been deposited in the zone of destruction on one side. Creevy expressed the opinion that healing may be said to have occurred only if pus and *Mycobacterium tuberculosis* have been recovered from a kidney which, at operation or necropsy after a considerable interval, contains a localized zone of destruction in which neither tuberculosis nor *Myco. tuberculosis* can be found. He did not believe that hygienic treatment is to be recommended as a substitute for nephrectomy except in an occasional case.

*Surgical Technic.*—Lazarus<sup>16</sup> described a maneuver designed to prevent injury to the diaphragm in cases of difficult nephrectomy. To reduce the period of con-

14. McClelland, J. C., and Davis, K. F.: The Relationship Between Skeletal and Genitourinary Tuberculosis, *J. Urol.* 47:320-322 (March) 1942.

15. Creevy, C. D.: An Example of Apparent Healing of Bilateral Minimal Renal Tuberculosis, *J. Urol.* 47:614-618 (May) 1942.

16. Lazarus, J. A.: A Simple Maneuver Designed to Prevent Injury to the Diaphragm in Cases of Difficult Nephrectomies, *J. Urol.* 47:109-111 (Feb.) 1942.

valescence to a minimum and to avoid injury to the diaphragm to which the capsule might be adherent, the surgeon divided the capsule surrounding the upper pole of the kidney, leaving it attached to the under surface of the diaphragm and removed the rest of the capsule along with the kidney, to which it is intimately adherent. The kidney is exposed by means of the usual Albarran incision, which should be of a length which is ample for good exposure and which will facilitate necessary manipulation. A pad is placed in the lower angle of the wound, and by means of a deep retractor placed over it firm traction is exerted downward toward the symphysis. By this maneuver the kidney is drawn downward into the wound. After Gerota's capsule has been incised, the kidney is exposed in its fatty capsule and freed as far as possible from its bed, care being exercised to make certain that the upper pole, which is intimately adherent to the diaphragm, is not disturbed. A transverse incision is made on the anterior surface of the kidney as close to the upper pole as visibility will permit. This incision is carried down through the entire thickness of the capsule to the renal cortex. The upper and lower edges of the incised capsule are then grasped with clamps, and by means of a grooved director a line of cleavage is found between the inner surface of the true capsule and the renal cortex. Once this plane has been reached, Lazarus said, it is possible to introduce the right index finger into this space and with one sweep dislocate the upper pole of the kidney out of its capsule. The posterior reflexion of the capsule is then divided with a sharp scalpel, so that thereby the upper pole of the kidney is completely decapsulated. The procedure is completed by removal of the kidney with the rest of the capsule, which is attached to it.

*Hypertension.*—To determine how often hypertension and unilateral renal disease are associated, Baggenstoss and Barker<sup>17</sup> studied the records of 97 patients who came to necropsy. There were 84 instances of unilateral renal atrophy and 13 instances of unilateral hypoplasia. There were 48 cases of pyelonephritic atrophy, 28 of hydronephrotic atrophy, and 8 of pyonephrotic atrophy. The size of the heart and the condition of the opposite kidney also were studied in each case. Only in the cases of pyelonephritic atrophy (39.6 per cent) and of pyonephrotic atrophy (37.5 per cent) was the incidence of hypertension greater than in the authors' control group (29 per cent). The highest incidence of hypertension (41.9 per cent) was noted in cases of pyelonephritic atrophy in which the kidney weighed 75 Gm. or less. Evidence of inflammation in the opposite kidney was present more often in cases in which hypertension was observed. The degree of arteriosclerosis in the opposite nonatrophic kidney was generally less severe than that in the atrophied kidney. Baggenstoss and Barker expressed the opinion that these results suggest that unilateral pyelonephritic atrophy is more often associated with hypertension than would be expected on the basis of chance, and that hypertension is more likely to be present if the atrophy is severe. They suggested further that in many cases in which hypertension is in an early or mild stage it may not be associated with renal arteriosclerosis.

Friedman, Moschkowitz and Marrus<sup>18</sup> studied data concerning 193 patients who underwent nephrectomy for unilateral renal disease. The mean blood pressure and the incidence of hypertension were no greater in this group than they were in comparable control series of patients. No correlation was noted between the type of renal disease present and the presence of hypertension. After removal of the diseased kidney the blood pressure of the majority of patients remained essentially unchanged, whether the patients had been hypertensive or normotensive before

17. Baggenstoss, A. H., and Barker, N. W.: Unilateral Renal Atrophy Associated with Hypertension, *Arch. Path.* 32:966-982 (Dec.) 1941.

18. Friedman, B.; Moschkowitz, L., and Marrus, J.: Unilateral Renal Disease and Renal Vascular Changes in Relation to Hypertension in Man, *J. Urol.* 48:5-15 (July) 1942.



operation. In 22 per cent of the patients who had had normal blood pressure before operation, hypertension developed postoperatively. A significant decline in blood pressure occurred in only 7 per cent of the patients who had had hypertension before nephrectomy. The incidence of hypertension was higher among patients who had good excretory function than it was among comparable patients whose excretion of urine from the diseased kidney was either poor or absent. Arteriolar sclerosis was found in the diseased kidneys of 82 per cent of the patients who had hypertension at the time of operation and of only 33 per cent of the patients who had a normal blood pressure at the time of operation but in whom hypertension developed after nephrectomy. The authors said that when unilateral renal disease and hypertension coexist, removal of the diseased kidney is not likely in the majority of cases to result in reduction of the blood pressure. The advisability of performance of nephrectomy in most cases should therefore be determined primarily by the nature of the renal disease rather than by the expectation that the blood pressure will be lowered thereby.

Shure<sup>19</sup> studied the incidence of hypertension among patients who had had pyelonephritis, his data consisting of those obtained in the performance of necropsy 11,898 times in a ten year period. Hypertension was found in 44.4 per cent of the cases, as compared with an incidence of 34.9 per cent in a control group of patients taken at random. After analysis, however, this greater incidence apparently related to patients who had bilateral pyelonephritis, and especially to men. It was most marked in relation to men more than 40 years old. The relative absence of high blood pressure among patients who had unilateral pyelonephritis was striking. The incidence of hypertension increased as the age of the patient increased, and was parallel to the incidence of advanced renal vascular damage. In small groups of patients who had polycystic kidney, horseshoe kidney and uncomplicated nephrolithiasis the incidence of hypertension was 46.15, 64.7 and 53.25 per cent, respectively.

In a review of renal disease as a factor in hypertension, Braasch<sup>20</sup> stated that of 4,000 patients who had hypertension, only 100 exhibited clinical evidence of a non-nephritic renal lesion. Only 19 of these patients, or less than 0.5 per cent of the total number of hypertensive patients, were selected for operation. He said that extensive investigation undertaken to rule out the kidneys as a cause of hypertension is not indicated unless there is definite clinical evidence of involvement of the urinary tract. Braasch found that chronic and atrophic forms of unilateral pyelonephritis, renal neoplasm, renal lithiasis, hydronephrosis, tuberculosis and polycystic kidneys, in the order given, are factors or causative factors in hypertension. The presence of renal stone or hydronephrosis, unilateral or bilateral, will not affect blood pressure unless there is secondary pathologic change in renal tissues. Best results from surgical treatment are obtained among young patients and when the hypertension is of comparatively recent origin. A permanent decrease in blood pressure was observed in only a third of the patients selected for operation. Braasch said there is no typical renal pathologic change observed in the presence of hypertension. The essential factor, in his opinion, is apparently an intrarenal vascular imbalance which permits the secretion of pressor substances.

Hyman and Schlossman<sup>21</sup> discussed the etiologic role of the intrarenal pelvis in hypertension. They found at necropsy of 55 patients who had had hypertension

19. Shure, N. M.: Pyelonephritis and Hypertension: A Study of Their Relation in 11,898 Necropsies, *Arch. Int. Med.* 70:284-292 (Aug.) 1942.

20. Braasch, W. F.: Genitourinary Surgery: Renal Disease as a Factor in Hypertension, *Am. J. Surg.* 56:209-215 (April) 1942.

21. Hyman, A., and Schlossman, N. C.: The Etiologic Role of the Intrarenal Pelvis in Hypertension, *J. Urol.* 48:1-4 (July) 1942.

that the incidence of intrarenal and that of extrarenal pelvis were similar. Review of 200 unselected intravenous pyelograms did not show that the incidence of hypertension among patients who had intrarenal pelvis was higher than it was among those who had extrarenal pelvis. In 71 patients who had renal calculi and hydro-nephrosis there was no relationship between the hypertension and the type of renal pelvis present. Hyman and Schlossman said that nephroptosis combined with an intrarenal pelvis does not appear to predispose to hypertension. They described experiments in which a quadrupedal animal with an intrarenal pelvis was placed in the upright position to simulate the relationships of the human kidney for a period of time sufficient for production of hypertension by other experimental means. The negative results of these experiments, as well as the results of studies of ureteral occlusion by other investigators, tend to show that the intrarenal pelvis does not play a causative role in clinical hypertension.

*Renal Disease and Surgical Risk.*—Odel<sup>22</sup> said that renal disease imposes an increased risk on the patient who comes to operation. In his general review of the subject, Odel pointed out the necessity for restoration of impaired renal function prior to surgical operation. Routine urinalysis and measurement of the volume of urine passed in twenty-four hours are valuable and simple preoperative tests. Determination of the concentration in the blood of urea, creatinine and chlorides, and determination of the carbon dioxide-combining power are valuable guides when renal impairment is more severe. Microscopic examination of the urine for erythrocytes, pus cells and organisms is indicated when renal infection is suspected. Mandelic acid and sulfonamide compounds are used in combating infection of the urinary tract. An increased oral or parenteral intake of fluid in the form of solutions of sodium chloride or of dextrose together with the use of theophylline with ethylenediamine promotes effective diuresis. Chlorides and sodium bicarbonate should be administered intravenously when they are indicated. The diet should be light and should contain a moderate amount of protein. Any patient who has renal disease and is to undergo an operation on the biliary or gastrointestinal tract should have the benefit of tests of hepatic function, Odel said. Spinal or local anesthesia is preferable from the renal standpoint. Postoperatively, measures must be taken to combat dehydration, oliguria, edema and anemia after the results of appropriate tests and determinations have established the causative factors of any of these conditions.

#### RENAL HYPERPARATHYROIDISM

Harrison<sup>23</sup> stated that urinary obstruction with imposed infection produces renal insufficiency, inducing hyperparathyroidism, with or without rickets, dwarfism or infantilism. Early recognition of the condition and relief from it achieved by the urologist are the only means thus far available to prevent this disease from progressing, Harrison said. It is of little benefit to the patient to remove obstruction, establish drainage and combat infection, when renal insufficiency has been established, with resultant changes. Harrison reported 5 cases, in 2 of which the patients died. Of the 3 patients who underwent operation and were living at the time of this report, 1 had a guarded prognosis with a solitary kidney and infection, and the other 2 were well and free of infection. One had attained a height of 6 feet (180 cm.) with no bony changes. The other had been growing at the rate of 2 inches (5 cm.) per year but was still stunted at the time of Harrison's report.

22. Odel, H. M.: Reducing the Surgical Risk in Patients with Renal Disease, *Nebraska M. J.* 26:343-347 (Oct.) 1941.

23. Harrison, F. G.: Urinary Obstruction in Children Inducing Renal Hyperparathyroidism, *J. Urol.* 48:44-57 (July) 1942.

## RETROPERITONEAL TUMORS AFFECTING THE KIDNEYS

Sweetser<sup>24</sup> discussed retroperitoneal tumors influencing the kidneys and ureters and reported 8 cases of these neoplasms. He said that an accurate diagnosis is difficult to make. Before the days of intravenous urography it was impossible in most cases to rule out the possibility of renal tumor and to arrive at a definite diagnosis. Sweetser said that the patient's discovery of a mass usually not associated with abnormalities of the urine and not having the characteristic mobility of an intraperitoneal mass would lead to the physician's suspicion of retroperitoneal tumor or cyst. As a rule, an exploratory operation would be performed with the diagnosis still in doubt. In some cases the patient's history and the results of physical examination should strongly suggest the diagnosis. Sometimes the results of urinalysis, studies of the blood and roentgenograms may help. The perirenal insufflation of air and other gases has been advocated for the making of contrast roentgenologic studies, but Sweetser said that this procedure is of limited value because it is sometimes misleading and is not without dangers. He said that it should be used only as a diagnostic last resort, and observed that he would rather not use it at all. He expressed the opinion that at present urography, intravenous and retrograde, anteroposterior and lateral, provides the most valuable information of any diagnostic technic, but even with that help the difficulty of diagnosis is still recognized. In reviewing the possibilities of diagnosis, Sweetser stated that the patient's history may be of little or no value or it may give the vital bit of information. Physical examination sometimes discloses a mass that is definitely separate from the kidneys and does not move with respiration. Sometimes, associated findings, such as an enlarged spleen or large lymph nodes situated elsewhere than in the renal region, may be a guide. Usually, the results of physical examination do not clinch the diagnosis. The results of laboratory studies may help, but usually do not. Roentgenographic studies are of greatest value, especially when the urinary tract and the gastrointestinal tract are outlined and viewed from front and side. Sometimes, even in these days, the diagnosis may have to be made by exclusion and may have to await exploratory operation or necropsy. Sweetser said that since as a rule the only hope of cure of a primary retroperitoneal tumor is surgical removal, an operation is usually justifiable and indicated. It is true, however, that complete removal of the tumor may prove to be impossible because of extension and involvement of the great vessels or other essential parts.

In most cases, by far, the transperitoneal approach has been used, although the mortality rate accompanying this procedure has been much higher than that which accompanies an extraperitoneal approach. The justification for the transperitoneal approach has been the better visibility and accessibility claimed for it, but Sweetser said that the transperitoneal operation is associated with a definite risk of peritonitis and results often in extreme surgical shock arising from handling of the bowels and peritoneal surfaces, evaporation and other factors incident to such a prolonged and difficult operation. On the other hand, the lumbar and flank incisions, which seem to be considered by most surgeons as the only alternatives, have admittedly been unsatisfactory in that they have not provided adequate visibility or accessibility.

## URETERS

*Stone*.—Kretschmer<sup>25</sup> reviewed a series of 500 cases of ureteral stone. He said that stone in the ureter is rare at the extremes of life. The youngest patient

24. Sweetser, T. H.: Retroperitoneal Tumors Influencing the Kidneys and Ureters, *J. Urol.* 47:619-631 (May) 1942.

25. Kretschmer, H. L.: Stone in the Ureter: Clinical Data Based on Five Hundred Cases, *Surg., Gynec. & Obst.* 74:1065-1077 (June) 1942.

in this series was 2 years old and the oldest 80. Stone occurred with the greatest frequency in the third, fourth, and fifth decades. Eighty-nine and four tenths per cent of the patients had a single stone, and only 53, or 10.6 per cent, had multiple stones. Stones in the ureter may vary in size, some being as small as a grain of wheat and others being of enormous size and weight. Hematuria may be the first and only symptom of which the patient complains. Furthermore, it should be remembered that stone is one of the five common causes of blood in the urine. In practically all the patients in this series, hematuria was followed by pain. Hematuria was present in 181 patients, or 34.2 per cent. The history of a previous passage of stones is most important. If a patient gives a history of having passed stones on one occasion or more, the odds are that he will pass stones again. Study of the roentgenologic findings in Kretschmer's series disclosed that positive reports for stone had been recorded concerning 455 patients, whereas the reports were negative concerning only 20 patients. Kretschmer said that the intravenous urogram is of much diagnostic aid. In the largest number of instances it reveals dilatation of the ureter and of the renal pelvis. Although dilatation (except when the stones are very small) is the rule, Kretschmer has seen a number of patients in whom the urograms disclosed no dilatation, despite the fact that the stones were far from being small. The urogram not infrequently reveals the ureter down to the bladder, or the outline may stop at the site of the stone, in this manner disclosing complete blockage.

A roentgenogram should be made of the renal region of each patient before operation; this procedure will avoid the embarrassment of the surgeon's operating only to find that the stone has progressed up the ureter or into the renal pelvis. Retrograde movement of the stone occurred in 10 patients in the present series. Kretschmer said that the treatment of stone in the ureter is naturally divided into three stages: (1) watchful waiting, (2) instrumental manipulation and (3) operative treatment. He said the fact should be borne in mind that many patients pass the stones without the use of instruments, by the simple expedient of drinking large quantities of fluids, with or without the taking of diuretic drugs. In Kretschmer's series 128 patients, or 28.9 per cent, passed stones without manipulation of any sort. He warned that manipulation of a stone with instruments is not entirely free from danger. In his series, 44.3 per cent of the patients passed the stone after manipulation. He said that during the past twenty-five years there has been a definite trend away from open operation in favor of cystoscopic manipulation. When a patient has a very large stone, it is perfectly obvious that manipulation is useless and that ureterolithotomy should be done at once. In case the patient has only two or three stones without complications, Kretschmer expressed the opinion that the urologist might wait or try manipulation before resorting to open operation. However, when complications are present, operation probably is the best procedure, although Kretschmer has seen patients with multiple stones pass them spontaneously. He said that a relatively large stone situated high in the ureter had best be operated for, whereas if a stone has descended into the pelvic portion of the ureter operation can be deferred while developments are awaited. If the onset of the symptoms is recent, the surgeon may wait, but if there have been recurrences without signs of remission, operation is clearly indicated.

In case severe reaction, such as pain, chills, fever and hematuria, occur after each instrumentation, the patient should be operated on. Operation is the only procedure to employ when severe attacks of hematuria, either with or without colic, occur and are accompanied by marked secondary anemia. On the other hand, when the patient has only an occasional loss of blood and mild secondary anemia, operation can be deferred to a later date. Kretschmer said that severe infection in

the kidney clearly indicates operation. Chronic pyelonephritis persists in the patients under consideration because of poor renal drainage, and should manipulation fail, operative removal of the stone is to be employed. Acute infection, unrelieved by drainage by ureteral catheter, necessitates operation at once. If the stone is large, this condition should be met with immediate removal; if the stone is small, drainage by ureteral catheter should be the procedure. In case drainage by catheter does not provide prompt relief, operation must be performed at once. Suppression of function above the anatomic situation of the stone does not call for immediate operation, since the opposite kidney will be able to maintain renal function. When complete hydronephrotic atrophy exists above the situation of the stone, operation should be performed. When moderately advanced hydronephrosis is present, the stone should be removed to prevent further progress of the hydronephrosis.

Cacciatore and Garcia<sup>26</sup> stated that there are many cases of ureteral lithiasis in which the results of routine roentgenologic examination of the urinary system are absolutely negative. They said that the frequency of occurrence of ureteral calculi that are invisible to roentgen rays is difficult to determine, since the literature on the subject is limited. In many papers the existence of such stones is mentioned and that is all. Cacciatore and Garcia protested against this manner of treatment of so important a subject, since the presence of a ureteral calculus is very different from the presence of a small caliceal or pelvic calculus. During the two years prior to the time of their report Cacciatore and Garcia systematically carried out intravenous urography on all patients who had renoureteral conditions. They regarded their results as of utmost importance in diagnosis. In 52 cases of ureteral lithiasis, 3 cases involved calculi which were invisible to the roentgen rays. This number represents 5.76 per cent, a figure the authors considered worthy of attention. In all 3 cases ureterolithotomy was carried out with excellent results. The means available for demonstration of these invisible stones are excretory urography, ureteral catheterization, retrograde pyelography and chromocystoscopy. Although these means of exploration may not permit visualization of the calculus, they will reveal the existence of "uroectasia" or retention of urine, the anatomic level at which the obstacle to evacuation is situated, its characteristics and the variations it undergoes from time to time. Cacciatore and Garcia said that if it is impossible to prove the existence of a ureteral calculus by direct visualization of the stone, an attempt should be made to demonstrate the dysfunction for which it is responsible. Among the types of dysfunction which may be present, uroectasia is the most frequent and the most important. Three illustrative cases were presented. They tend to show how misleading it is, on the basis of a plain roentgenogram of the urinary system, to consider the result "negative" when a calculus cannot be seen in the urinary system. On the other hand, the extraordinary value of excretory urography in cases of invisible calculus of the ureter is demonstrated, as is also the relative value of this form of exploration in cases in which the renal function, already seriously compromised, does not permit elimination of the opaque substance. The indispensability of ureteral catheterization and retrograde pyelography is also emphasized as a means of determining the precise localization of the ureteral obstruction and its character. Pneumopyelography is useless, since there is no air space around the calculus. All the observations gained from the aforementioned modes of exploration are important in cases of an obstructive renoureteral syndrome. Failure to make an exact diagnosis may lead to useless and even disastrous forms of therapy. Expectant therapy is especially condemned, because it may be responsible for irreparable damage to a kidney.

26. Cacciatore, C., and Garcia, A. E.: Los cálculos ureterales no visibles a los rayos X, *Rev. argent. de urol.* 10:681-707 (Nov.-Dec.) 1941.

Muschat<sup>27</sup> discussed suprapubic ureterolithotomy. He uses a midline incision, which he has found gives satisfactory exposure with more safety and which consumes much less time than operations carried out by the old method of approach. In 1 case he removed two stones, one from each ureter, through the same incision. To do this by the old method he said, would have required two separate operations. A midline suprapubic incision is made which extends from the pubis to the umbilicus. The fascia is cut, and the rectus muscles are exposed and split, freed and retracted. The bladder is picked up with forceps and retracted to the opposite side. By blunt dissection, the upper corner of the bladder is free from the surrounding structures. The ureter is located in the upper end of the wound and can be picked up just as it leaves the covering of the peritoneum and becomes a free pelvic structure. This procedure is followed down to the ureteral vesical junction. A simple incision in the ureter is then made, and the stone is removed. The postoperative course usually is smooth, and there is very little abdominal or gastric reaction, probably because the peritoneum remains practically untouched.

*Ureterointestinal Anastomosis.*—Riba<sup>28</sup> reported a case of ureterointestinal anastomosis with an unusual complication. The patient was a girl 8 years old, who had exstrophy of the bladder. The ureter from the one good kidney (the right one) was transplanted to the colon. The left kidney was small and pyonephrotic and was removed. Two years after the second stage ureteral transplantation, the patient became uremic and very sick. The value for nonprotein nitrogen was elevated. Nephrostomy (right side) was performed, and a catheter was placed in the lower calix. The patient recovered from this operation readily. Later, a proctoscopic examination revealed that the site of the ureteral transplantation had become invaginated into the bowel. With an electric meatotome, this invagination or "rectal polyp" was incised, and this permitted the urine to pass freely through the anastomosis. The nephrostomy tube was then removed, and excretory pyelograms disclosed good function in the right kidney.

*Ureterocele.*—Thompson and Greene<sup>29</sup> reported a clinical study of 37 cases of ureterocele. In most cases this condition is of congenital origin, and it occurs much more frequently among women than among men. The ages of the patients varied from 9 to 64 years; the majority were between 30 and 50 years. The most common symptoms were pain, frequency of urination, dysuria, hematuria and passage of calculi. The diagnosis can always be determined by cystoscopic examination and only in an occasional case by excretory urography. The most satisfactory treatment, the authors said, is fulguration of the contracted ureteral orifice or a combination of ureteromeatotomy and fulguration of the wall of the ureterocele. Open operation is necessary in the presence of destroyed renal function or of urinary calculi which cannot be removed by transurethral methods.

*Polyps.*—Johnson and Smith<sup>30</sup> reported a case in which ureteral polyps had developed in a man 24 years old. The pyelograms disclosed hydronephrosis in the upper portion of the left ureter. There was a tear-shaped negative shadow on the basis of which the diagnosis of ureteral polyp was made. On surgical exploration the polyps could be felt just below the ureteral pelvic juncture. Nephrectomy was done, and the polyps were found to be similar to those occasionally seen in the nasopharynx.

27. Muschat, M.: Suprapubic Ureterolithotomy, *J. Urol.* **47**:571-576 (May) 1942.

28. Riba, L. W.: Late Uretero-Intestinal Anastomosis Complication: Case Report, *J. Urol.* **47**:679-685 (May) 1942.

29. Thompson, G. J., and Greene, L. F.: Ureterocele: A Clinical Study and a Report of Thirty-Seven Cases, *J. Urol.* **47**:800-809 (June) 1942.

30. Johnson, C. M., and Smith, D. R.: Benign Polyps of the Ureter, *J. Urol.* **47**:448-452 (April) 1942.

*Diverticulum.*—Richardson<sup>31</sup> reported a case in which diverticulum of the ureter afflicted a woman 39 years old. The diverticulum originated from the middle third part of the ureter well below the renal pelvis and above the brim of the bony pelvis. There was no history of trauma to the ureter, infection of the urinary tract at any time, hematuria, passage of calculi or either renal or ureteral colic. At operation a no. 8 ureteral catheter was readily passed through the lower segment of the ureter into the bladder without meeting obstruction. Richardson said that repeated postoperative cystoscopic studies have demonstrated only that slight narrowing of the bladder segment of the ureter may be present, a narrowing which, however, permits the easy passage of ureteral catheters. It seems probable, therefore, that this diverticulum was of congenital origin. Its enormous size (3,500 cc. of urine by accurate measure was evacuated at operation) places it in a class by itself. Furthermore, Richardson said, his case is the only recorded instance of diverticulectomy in which double division of the ureter was required. It is also the only recorded instance in which after diverticulectomy an immediate and successful end to end anastomosis of the ureter was carried out, with subsequent restoration of function to normal. Richardson also reviewed the published clinical reports on this condition and summarized the data which they supply. He said that in the matter of priority, Lotsi was the first to report a diverticulum of the ureter in a living person; Neff shares with Hale and von Geldern the honor of having first diagnosed the condition with certainty prior to operation; and Teposu and Danicico were the first to demonstrate this lesion by means of excretion pyelography.

Of the recorded patients, 2 were less than 3 years old; 1 was 10 years old; 2 were in the second decade of life; 10 were in the third decade; 7 were in the fourth decade; 4 were in the fifth decade, and 2 were in the sixth decade. Richardson said that the sex was stated in 30 instances; in 15 cases the patients were male and in 15 they were female. The right side was involved in 13 cases, the left side in 14 and both sides in 1. In 17 cases the diverticulum was situated within 5 cm. of the site of the insertion of the ureter into the bladder; in 7 it was located from 5 to 10 cm. above the bladder; in 6 it had arisen adjacent to or within 4 cm. of the ureteropelvic junction. Preoperative diagnosis appears to have been made with reasonable accuracy in 28 cases by means of roentgenologic studies, cystoscopic investigations, including catheterization of the ureters, and retrograde pyeloureterography. In only 3 instances was a preoperative diagnosis arrived at by the use of excretion pyelography. Calculi were found in 8 of the diverticula. The formation of these calculi was promoted by infection and stagnation. Twenty patients had pain, colicky or dull, on the involved side; 19 had pyuria; 17 had frequency of micturition and dysuria; 6 had nausea and vomiting; 4 had hematuria; 4 had chills and fever. Richardson said there is, however, no characteristic syndrome. Treatment varied according to the requirements of and indications in the individual patient. For a few patients repeated dilation of ureteral strictures sufficed. Others required ureterotomy with dilation of the ureteral orifice. The majority, however, required a more radical procedure, such as diverticulectomy, diverticulectomy together with reimplantation of the ureter into the bladder, or nephroureterectomy. On the whole, the results have been satisfactory and creditable.

31. Richardson, E. H.: Diverticulum of the Ureter: A Collective Review with Report of an Unique Example, *J. Urol.* 47:535-570 (May) 1942.

*Spasm.*—Lazarus and Marks<sup>32</sup> stated that ureteral spasm is a frequent finding in urologic practice. It may occur spontaneously or it may be associated with or initiated by a variety of conditions, among which ureteral calculus is the most frequent. It may occur in one ureter or both, either as a primary condition or as a secondary manifestation from some source of irritation which may be present on one side or both sides. Contralateral spasm presents an interesting and not infrequent condition occurring among patients who have unilateral renal or ureteral disease and may give rise to mild or severe symptoms. Relief of obstruction in one kidney usually results in spontaneous relaxation of the spasm in the opposite ureter.

#### BLADDER

*Fistula.*—Barnes and Hill<sup>33</sup> reported a series of 14 cases of intestinovescical fistula. The most common cause of this condition is diverticulitis of the large bowel, and the fistula and its underlying pathologic process frequently are not found, the patient being treated for what is thought to be "cystitis." Passage of gas from the bladder is almost diagnostic, and the cystoscopic appearance of a zone of edema and inflammation in the fundus of the bladder is the most characteristic observation. Cystograms, roentgenologic examination of the bowel and instillations of a dye may prove to be unsatisfactory as aids to diagnosis. Proctoscopic examination is preferable to roentgenologic study for the diagnosis of lesions in the terminal 10 inches (25 cm.) of the bowel. Surgical treatment is sometimes difficult, and the performance of preliminary colostomy is usually but not always preferable. Treatment should be administered for the prevention of postoperative peritonitis.

Counseller<sup>34</sup> called attention to the difficulty of closure of small vesicovaginal fistulas in certain situations, with particular regard to the vesical sphincter and ureters. Sulfanilamide and its derivatives have enhanced the treatment of vesicovaginal fistula in that the drug and its derivatives are able to destroy organisms in the urine in a much shorter period than had been possible formerly. It is thus possible to maintain the urine in a nearly sterile state during convalescence of the patient. This has been a very great asset in the improvement of end results. Meticulous care must be devoted to the patient during convalescence, to maintain the urine free from infection and to avoid incrustation in the bladder and occlusion of the catheter. The vagina should be cleaned of secretions daily. Ureterosigmoidostomy has a definite place in the treatment of huge vesicovaginal fistulas in cases in which the bladder has been rendered incapable of again retaining urine. Rectovaginal fistulas are best treated by complete excision of all scar tissue and reestablishment of the normal character of the rectum. Counseller expressed the opinion that particular attention should be directed toward those small fistulas which originate in an anal crypt, a circumstance in which it is essential that the surgeon understand the cause of the condition and the clinical course of the patient. Postoperative care is similar to that for patients who have undergone repair of vesicovaginal fistulas in that suture lines in both the rectum and vagina must be kept clean daily. This can be done by the use of a Sims speculum, a small anoscope and dry cotton swabs. Attention to these details will greatly increase the number of instances of primary healing.

32. Lazarus, J. A., and Marks, M. S.: Ureteral Spasm with Special Reference to Contralateral Spasm of the Ureter: A Clinical Study, *J. Urol.* 48:69-82 (July) 1942.

33. Barnes, R. W., and Hill, M. R.: Intestino-Vesical Fistula, *California & West. Med.* 56:350-354 (June) 1942.

34. Counseller, V. S.: Surgical and Postoperative Treatment of Large Vesicovaginal and Rectovaginal Fistulas, *Surg., Gynec. & Obst.* 74:738-745 (March) 1942.



Counseller<sup>35</sup> also discussed the various types of vesicovaginal fistulas in respect to some of the surgical problems involved in their repair. He said that the most important preoperative measure is cystoscopic examination of the bladder for determination of the amount of infection present, the direction of the fistula and its situation with respect to the trigone, urethral sphincter and ureteral meatuses. Postoperative care should include special measures, such as placing of the patient in the prone position on a Bradford frame above the surface of the bed, daily irrigation of the bladder and cleansing of the vagina. Culture of the urine should be done frequently in order to determine the bacterial count. Sulfathiazole and mandelic acid are extremely beneficial in the control of infection of the urinary tract.

Masson and Wilson<sup>36</sup> reported the results of their experience in the care of 48 patients who had a fistula between the urinary tract and vagina for which surgical repair was undertaken and 13 patients for whom operation was not performed. These patients were encountered from January 1937, to December 1939, inclusive. Thirty-three (69 per cent) of the 48 fistulas developed after surgical procedures and 13 (27 per cent) after childbirth. The surgical procedures included abdominal hysterectomy (23 cases), vaginal hysterectomy (3 cases), chemical hysterectomy (1 case), and other operative procedures (6 cases). In 1 case the condition had been caused by radium treatment, and in another, by congenital fistula. A vesico-vaginal fistula was present in 40 cases, urethro-vaginal fistula in 2 cases, uretero-vaginal fistula in 2 cases and uterovesical fistula in 4 cases. That the condition may be difficult to cure is shown by the fact that 29 of the patients had undergone ninety operations, or more than three per patient, before they were seen at the Mayo Clinic. Only 19, or less than 40 per cent, had not undergone a previous operation. At the Mayo Clinic 38 (79.2 per cent) of the 48 patients underwent one operation and 7 (14.7 per cent) underwent two operations. Three patients underwent more than two operations. Masson and Wilson employed vaginal closure in 41 (85.5 per cent) of the cases. Abdominal closure was employed in 3 cases, transplantation of the ureter in 2 cases, and nephrectomy in 2 cases. Forty-two of the patients were cured by the operative procedures. One operative death occurred in this series. In the operative technic employed by Masson and Wilson emphasis is placed on the following points: (1) prone position of the patient, with the buttocks elevated during the operation; (2) adequate exposure, and (3) adequate mobilization of the vaginal flap and of the bladder, with closure with interrupted sutures without tension. The vesical and vaginal openings are closed separately in opposite directions. Postoperative insurance of continuous drainage of the bladder is accomplished by placing of the patient in the prone position on a Bradford frame.

**Carcinoma.**—Of 279 patients with tumor of the bladder treated with radon implants, Herger and Sauer<sup>37</sup> were able to trace 229 as to developments, clinical course and duration of radium reactions. Although late effects of radium therapy, such as telangiectases or stricture of the ureter, occurred infrequently, ulceration was observed in 195 (80.7 per cent) of the cases. In 53 instances such ulceration was complicated by the development of incrustations or stones or both. One

35. Counseller, V. S.: Some Urologic Phases of Vesicovaginal Fistula, *J. Urol.* 47:711-720 (May) 1942.

36. Masson, J. C., and Wilson, R. B.: Fistulas Between Urinary Tract and Vagina, *Minnesota Med.* 24:637-644 (Aug.) 1941.

37. Herger, C. C., and Sauer, H. R.: Occurrence and Clinical Course of Radium Reactions Following Use of Radon Implants in Treatment of Carcinoma of Bladder, *J. Urol.* 47:141-147 (Feb.) 1942.

hundred and three of the ulcerations healed and 92 persisted either until death of the patient or until the time of the authors' report.

The statistical data presented indicate that the tendency toward the formation of ulcers is least with low grade malignant papillary carcinomas and greatest with papillary tumors of a high grade of malignancy, as well as with solid infiltrating cancers. Aside from the histologic aspects, the location of the lesion is important. Tumors which originate in the region of the vesical sphincter or center and border of the trigone have a substantial tendency toward the formation of persistent ulcers, whereas lesions of the anterior and posterior walls of the bladder are associated with a better prognosis as to development and healing of radium ulcerations.

For the determination of factors which influence the clinical course and duration of radium ulcerations, data on 179 patients who had single tumors were collected. The results of these studies show that the tendency toward persistence of radium ulcerations is in direct proportion to the size of the zone of implantation and to the amount of radium therapy delivered. The percentage of persistent ulcerations was 62.5 per cent for zones of from 4 to 5 cm. and 71.4 per cent for lesions larger than 5 cm. in diameter. If more than 300 millicurie hours of treatment was delivered to the tumor, persistence of the ulcer was observed in two thirds of the cases. The average duration of radium ulcerations among patients in whom healing of the ulcer took place was ten and six-tenths months. It was found that the duration of the ulceration was in direct proportion to the size of the zone of implantation and to the amount of interstitial radium therapy delivered. Radium ulcerations of the anterior and posterior walls of the bladder healed faster than those located in the fixed parts of the bladder. The development of incrustations or stones also prolonged the duration of the radium ulcers.

Barringer<sup>38</sup> reported that cancers of the bladder, both papillary and infiltrating, are well adapted for therapeutic attack by means of radon implants. Of 257 patients examined up to and including 1937, 112 had papillary cancers and 145 had infiltrating cancers. Excluding 15 patients, in most of whom metastasis had developed and palliative operation had been performed, 56.1 per cent of patients who had papillary cancer and 28.9 per cent with infiltrating cancers had been well for five years at the time of Barringer's report. When the two groups were combined, a five year rate of cure of 40.4 per cent was obtained. Both the suprapubic and the cystoscopic route have been used for the application of radon seeds, the latter route in about a fourth of all cases. The chief complications arising from the implantation of radon seeds are infection and formation of stones. These complications are becoming fewer as modifications are made in the original technic of implantation. Tumors of the vault of the bladder and extensive papillomatosis are better treated by means of operation alone. With all other types of cancer of the bladder radon implantation is more simple to effect, is associated with a lower operative mortality rate and provides more assurance of five year cure, Barringer said.

Fleischman and Mauritz<sup>39</sup> stated that adenocarcinoma of the urinary bladder is a rare pathologic entity. They said that Ash, in a careful analysis of 2,000 cases in the bladder tumor registry maintained by the Army Medical Museum for the American Urological Association, reported only 2 cases of this particular type of carcinoma. Two types of adenocarcinoma are recognized: (1) without colloid

38. Barringer, B. S.: Five Year Control of Bladder Cancers by Radon Implants, *J. A. M. A.* 120:909-910 (Nov. 21) 1942.

39. Fleischman, A. G., and Mauritz, E. L.: Adenocarcinoma of the Urinary Bladder, *J. Urol.* 47:658-663 (May) 1942.

degeneration and (2) with this type of degeneration, the latter being the type most frequently observed. The general characteristics of these tumors are not always the same. They vary in size, are usually sessile, appear frequently as flat, indurated lesions with ulcerated or necrotic zones and invariably infiltrate the deeper tissues. Histologically colloid adenocarcinomas are characterized by acini whose cell linings are of the high cylindric variety with basal nuclei which exhibit various stages of formation of mucin. Masses of mucin may be seen lying in the free spaces formed by the fibrous tissue. Fleischman and Mauritz said that the clinical observations made on a patient suffering from adenocarcinoma of the bladder differ in no way from those associated with neoplasms that are frequently found in the bladder, hematuria being the cardinal symptom. The usual dysuria and urgency and frequency of micturition invariably are present also. However, the clinical history may differ from that of other vesical neoplasms if the tumor has not penetrated the mucosa. An abdominal mass may be felt in the area of the bladder if the tumor is of unusual size. The authors said that such a tumor has been reported by Barringer. A tumor situated in the region of the trigone or vesical neck can be treated transurethrally. One situated at the apex of the bladder unquestionably cannot be removed satisfactorily by this method. It must be removed by suprapubic radical excision. Fleischman and Mauritz reported a case in which adenocarcinoma of the urinary bladder occurred in a white man 36 years old. The tumor was removed by means of the electrosurgical cautery. Extravesical extension was found later, and the patient died seven months after the operation.

*Hemangioma.*—Kahle, Maltry and Vickery<sup>40</sup> reported a case in which hemangioma of the bladder occurred in a woman 52 years old. At cystoscopic examination a papillomatous mass 1 cm. in diameter was seen in the region of the right ureteral orifice. A similar tumor was seen just above the trigone. The tumors were removed through a Stern-McCarthy resectoscope. The histologic report was "benign ulcerating angioma."

*Glandular Proliferation.*—Emmett and McDonald<sup>41</sup> stated that proliferative lesions of the urinary bladder which simulate tumor are occasionally encountered. Grossly, these lesions may closely resemble carcinoma, but histologic examination will show them to be composed of a proliferation of glandular tissue usually associated with inflammation. Emmett and McDonald, in the cases they studied, recognized two distinct types of glands: (1) the subtrigonal type (also called glands of Albarran), and (2) glands simulating those found in the intestine, which they called the "intestinal" type of glands. They said that the lesions seen in such cases have been described by many names, the most common of which is "cystitis glandularis." These glands are not apparent in the urinary bladder at birth and appear to be formed by metaplasia from the epithelium lining the urinary bladder. The presence of infection in all but 1 of the cases presented by the authors suggested that it is an important factor in the production of these glands.

*Calculus.*—Prentiss<sup>42</sup> presented a clinical analysis of two groups of similar patients who were suffering from vesical calculus treated by means of cystolithotomy or lithotripsy. He said the development of transurethral surgery has

40. Kahle, P. J.; Maltry, E., and Vickery, G.: Hemangioma of the Bladder: Report of an Additional Case, *J. Urol.* 47:267-269 (March) 1942.

41. Emmett, J. L., and McDonald, J. R.: Proliferation of Glands of the Urinary Bladder Simulating Malignant Neoplasm, *J. Urol.* 48:257-265 (Sept.) 1942.

42. Prentiss, R. J.: Vesical Calculus: Clinical Study Based on Two Hundred and Fifty Cystolithotripsies and One Hundred and Thirty-Two Cystolithotomies, *J. Urol.* 47:664-671 (May) 1942.

eliminated most of the technical contraindications to lithotripsy and also all objections that the operation does not remove the associated obstructive causative factors of stone. The much reduced hospital stay and mortality rate, as well as the ease with which associated local conditions can be treated by means of the transurethral operation as compared with open attack on vesical calculus, justifies the readoption of the transurethral procedure as a proved, conservative method, Prentiss said.

Garcia<sup>43</sup> reported a case in which a man had a vesical calculus that had formed around a silk suture which had been placed in the wall of the bladder eight months previously, at the time of an operation, performed by another surgeon, for repair of inguinal hernia on the right. The patient described, with precise details, the placing of an indwelling urethral catheter at the close of the aforesaid operation, and the appearance of chills and fever in the days following, with pain in the hypogastrium and frequency of urgency to urinate, despite the presence of the catheter. Intense hematuria had been present for a week. At the end of two weeks, the signs of infection had disappeared, the pain had diminished and the urine was normal in appearance. The patient said he had been discharged after four weeks in the hospital, but micturition had not been normal since that time. Persistent pollakiuria with burning and tenesmus had been present since his discharge from the hospital. A plain roentgenogram of the bladder disclosed an oval shadow characteristic of a vesical calculus. When lithotripsy was attempted, it became apparent that the calculus was attached to the posterosuperior wall of the bladder, and this attachment made it difficult to grasp the stone. An attempt at traction produced hemorrhage, which prevented further endoscopic intervention. On the fourth day, the left epididymis became inflamed and a small abscess was found to require drainage. Two weeks later the calculus was removed from the bladder by cystotomy. It was found to be fixed to the right lateral wall of the bladder by a filiform pedicle. On extraction the stone was found to be 5 cm. in length; it closely resembled a snail, and was composed of three calculous masses, each distinct from the other and movable but all united by a flexible axis, along which they were strung. This axis, protruding at one end, was nothing other than the fragment of silk which had been placed, in a continuous suture, in the wall of the bladder to close a wound inflicted accidentally during herniorrhaphy eight months previously. That the suture was continuous could be shown clearly by the type of its uncovered terminus, the entire axis being more than 7 cm. in length. Garcia expressed the opinion that the case shows the untoward results that may follow the use of a nonabsorbable suture in a wound of the bladder and also the danger involved in the placing of a continuous suture in this structure. But whether a continuous suture is used or separate sutures are chosen, the outstanding lesson is that absorbable material should be employed. Otherwise, there is danger that the suture may serve as a foreign body around which, as a nucleus, mineral salts may collect.

*Rupture.*—Culp<sup>44</sup> discussed the treatment of ruptured bladder and urethra. He reviewed 86 cases of extravasation of urine, and made the therapeutic recommendations which follow.

Retrograde cystograms should be made in all cases in which rupture of the bladder is suspected and the correct diagnosis is not obvious. Physical observations

43. Garcia, A. E.: *Cálculo vesical secundario a la sutura de la vejiga con material no reabsorbible*, Rev. argent. de urol. 10:709-716 (Nov.-Dec.) 1941.

44. Culp, O. S.: *Treatment of Ruptured Bladder and Urethra: Analysis of Eighty-Six Cases of Urinary Extravasation*, J. Urol. 48:266-286 (Sept.) 1942.

alone may be disastrously misleading. Prompt operation, preferably carried out within two hours of the onset of extravasation, is imperative. Drainage by urethral catheter alone did not suffice to produce recovery for any patient who had the condition under consideration. Operation should consist of routine exploration of the peritoneal cavity, cystostomy and drainage of the perivesical tissues to as far as the base of the bladder. Culp said that the most common cause of death is peritonitis for which surgical exploration is not carried out. Retroperitoneal extravasation of urine was encountered frequently, but in such cases it was rarely possible to establish adequate drainage. The defect in the wall of the bladder should be repaired if possible, but this is not essential. The peritoneal cavity can be closed without the establishment of drainage after the evacuation of extravasated fluid, but drainage through stab wounds is the safer procedure. Rupture of the posterior urethra must be suspected in all cases of fracture of the pelvis. Complete division of the urethra at the prostatic apex is the most common type of injury. Cystourethrograms should be made in all cases in which the diagnosis is doubtful. Suprapubic drainage (established within four hours, if possible) should be routine. Retroperitoneal extravasation in which drainage was inadequate was the most common cause of death. Perineal anastomosis of the urethra or retrograde catheterization facilitates recovery. Culp said that urethral strictures must be dilated with care. In his series such instrumentation was responsible for most perforations of the anterior portion of the urethra. It is safer to use filiform bougies and followers than it is to use sounds. The contents of all periurethral abscesses should be drained, in view of the incidence of inflammatory perforation and subsequent extravasation of urine. Extensive drainage of regions in which extravasation has occurred and provision for adequate drainage of urine should be established within twenty-four hours of the onset of extravasation. Traumatic and inflammatory perforations present the same surgical problems. Perineal urethrotomy and suprapubic cystostomy (with or without retrograde catheterization of the urethra) are most valuable. Combined injury to the anterior and posterior portions of the urethra should be suspected in all cases of perforation near the triangular ligament. Suprapubic drainage should be instituted if any doubt arises as to pelvic involvement. Sulfonamide compounds should be administered orally and locally to all patients who can tolerate these drugs. Fluids should be administered intravenously in liberal quantities (judiciously) to combat or to prevent uremia and acidosis, which frequently complicate extravasation of urine.

#### CONGENITAL OBSTRUCTION OF THE NECK OF THE BLADDER

Thompson,<sup>45</sup> in discussing urinary obstruction of the vesical neck and posterior portion of the urethra of congenital origin, stated that the symptoms arising from congenital malformation of the vesical neck or posterior urethra seldom are apparent at birth. The onset of obstruction is insidious, and gross distention of the bladder does not appear early in the course of the disease. The urologist should suspect the presence of the condition while the amount of retained urine is still small. Renal insufficiency is a late manifestation. Recurring episodes of infection of the urinary tract should excite suspicion. Urographic evidence of obstruction will help to establish the diagnosis while renal function is still adequate. Thus, valuable glomeruli can be preserved. Thompson said:

The deformity usually noted on cystoscopy is some condition other than valvular formations. The obstruction may be slight and the cystoscopist should look for the effects of obstruction,

45. Thompson, G. J.: Urinary Obstruction of the Vesical Neck and Posterior Urethra of Congenital Origin, *J. Urol.* **47**:591-601 (May) 1942.

such as trabeculation of the wall of the bladder, ureteropyelectasis and the like, rather than extreme deformity of the vesical neck or of the posterior urethra. Excision or destruction of what seems to be a minimal amount of tissue often will produce amazing results.

The postoperative treatment of infection is of paramount importance. The accumulation of residual urine cannot always be immediately abolished; great improvement in the tone of the detrusor muscle gradually will develop. It is best not to reoperate in any case until after edema incidental to operation has subsided. Catheterization during this period is sometimes necessary. Chemotherapy employed intermittently for a number of months postoperatively is best. Great improvement in the general health of the patient, restoration of normal urination and complete elimination of infection are possible when renal function has not been long impaired. Children affected by the condition are not always condemned to an early death, as has been alleged by some.

#### PROSTATE GLAND

*Hypertrophy.*—In another report Thompson<sup>46</sup> stated that transurethral prostatic resection is superior to other types of surgical treatment of the prostate gland. Recent developments in the resectoscope and better training of surgeons, he said, have eliminated objections to this method. In fact, so-called total prostatectomy can be more nearly accurately and effectively carried out through the urethra than by any other approach or means, with far fewer complications and a much lower mortality rate. Thompson reported on a series of 1,000 patients with various types of prostatic obstruction who were operated on by this method at the Mayo Clinic in 1939. In 40 cases two operations instead of one were necessary. Only 3.4 per cent of the 1,000 patients were less than 50 years of age, the average age being about 70 years. Heart disease was found in 22.8 per cent of the cases and hypertension in 28 per cent. Renal insufficiency was present in about a fourth of the cases. In 69.4 per cent of the cases the patient's postoperative temperature did not exceed 100 F. (37.7 C.). From the average patient who presented the ordinary type of prostatic enlargement the amount of tissue removed was 34.9 Gm. Thompson stated that the postoperative hospital stay is decidedly shorter than that required after other types of prostatic surgery have been carried out, and that complications occur infrequently. Of the 1,000 patients concerned, only 9 died; thus the mortality rate was less than 1 per cent.

Owens<sup>47</sup> compared the results of perineal prostatectomy and transurethral resection. He declared that the value of the transurethral method of prostatic surgery is now generally accepted. It has offered, he said, the first real challenge to the perineal approach for honors in the field of low mortality rates in surgical treatment of the prostate gland. The mortality record for perineal prostatectomy, when the operation has been properly done, has always been enviable; likewise, the late results of this operation have been excellent; but in the days when open operation was the only choice too many patients delayed their coming to the surgeon until their tissues were beyond recovery, even though the most skilful care might have been available. Owens said that thanks to transurethral resection the patient's fear of seeking relief has been removed, and, now that patients do come to the surgeon earlier than before, the type of care most suitable to their individual condition can be given them.

46. Thompson, G. J.: Transurethral Prostatectomy, *Urol. & Cutan. Rev.* 45:755-757 (Dec.) 1941.

47. Owens, C. A.: Perineal Prostatectomy and Transurethral Resection: A Comparison of Results, *J. Urol.* 47:366-371 (March) 1942.

Thompson<sup>48</sup> discussed the subject of the patient with disease of the prostate who has marked renal insufficiency and in whom the content of urea in the blood is well over 100 mg. per hundred cubic centimeters. Such patients, he said, arrive with a greatly distended bladder but are still able to void. For this reason the bladder has not been drained previously, and in some instances the patient is unaware of the hugely distended bladder. Many times symptoms unrelated to the urinary tract cause them to seek medical attention. Often secondary anemia, weakness, drowsiness and vomiting are the presenting symptoms rather than difficulty arising from the urinary system. Thompson stated that in examination of such a patient the less trauma inflicted on the bladder and prostate gland the better, and said that he avoids making cystourethrograms or carrying out cystoscopy or retrograde pyelography. As a rule, a soft rubber catheter is used to drain the bladder; usually an inlying catheter or catheterization every six or eight hours constitutes a better method of treatment. The great majority of patients, however, can tolerate an inlying catheter, and such is the type of drainage employed until the output of urine is on the increase and there is great general physical improvement.

One patient with prostatic obstruction had a value for blood urea on admission of 410 mg. per hundred cubic centimeters. After two weeks of drainage by catheter, and with an output of urine of 3,500 to 4,000 cc. daily, the value for urea was still 160 mg. per hundred cubic centimeters. At this time transurethral prostatic resection was done, and 45 Gm. of tissue was removed in the usual manner. The patient's subsequent convalescence was smooth, and he left the hospital on the tenth post-operative day, at which time the value for blood urea had decreased to about 100 mg. per hundred cubic centimeters.

Thompson said he has not employed suprapubic cystostomy in these cases because in his opinion carefully managed drainage by urethral catheter can be carried on with less hazard to the patient than the aforementioned operation. In some cases secondary anemia is so advanced that it is necessary to transfuse blood before operation. He does not routinely employ any preoperative medication. If sulfonamide compounds are used they must be administered cautiously, for when renal function is greatly reduced the concentration of the drug in the blood usually increases rapidly. Thompson expressed the belief that the best type of anesthesia as a rule is low spinal anesthesia. However, in some instances in which the anemia has been extreme he has employed instead intravenous anesthesia produced with pentothal sodium. Drainage by catheter for five or six days postoperatively has been deemed wise. Because of the flaccidity of the bladder in these cases, it has been his rule to catheterize the patient six hours after the inlying catheter has been removed. In general, no matter how complete resection may be, retention of varying degrees is present for a number of days after removal of the catheter. For instance, a patient who had retained 5,400 cc. of urine had no desire to void for the first six or seven hours after the catheter had been removed. Finally, he voided a very satisfactory stream, but catheterization disclosed 600 cc. of retained urine. In the subsequent week the amount of retained urine gradually diminished to less than 60 cc. Shortly before publication of this report, Thompson received a letter from the patient's son (a physician), in which it was stated that the patient had no retention and that the urine was crystal clear.

The mortality rate in cases of this type is approximately the same as in cases in which an average condition is encountered. Thompson discussed the decrease

<sup>48</sup> Thompson, G. J.: Prostatic Hypertrophy with Marked Renal Insufficiency, Urologists' Correspondence Club, Oct. 26, 1942.

in blood urea after transurethral removal of the prostate gland. In several patients the value for blood urea remained at from 80 to 90 mg. per hundred cubic centimeters even after six months' drainage by suprapubic cystostomy. However, when the prostate gland was enucleated, the value for urea immediately decreased to a value well below that which had obtained even with perfect drainage through the cystostomy tube. Probably the best explanation for this is that any type of artificial drainage is inferior to natural drainage.

Russ<sup>49</sup> presented 2 cases of prostatic obstruction in which the symptoms were predominantly gastrointestinal. He emphasized the fact that many lesions of the genitourinary tract may cause gastrointestinal symptoms which often lead to a delayed or an erroneous diagnosis. Thompson, in discussing these cases, stated that when the physician is confronted by an elderly man with bizarre symptoms he should always think of the possibility of urinary retention and resort to catheterization on the slightest indication.

#### PROSTATIC RESECTION FOR PATIENTS WITH TABES DORSALIS

Emmett and Beare<sup>50</sup> stated that bladder difficulties of tabetic patients are poorly understood. They reviewed the records of 419 patients who complained of such difficulties. Among males, aside from incontinence and the inability to determine when the bladder was full, the symptoms were similar to those caused by uncomplicated obstruction of the vesical neck. After studying the amount of residual urine in the bladder, Emmett and Beare concluded that in not more than 50 per cent of cases could the incontinence be attributed to overflow. Relaxation of the vesical neck was more common among the patients who had urinary incontinence, but with this single exception, the cystoscope disclosed nothing in their condition that was different from the condition of other patients in this group. Ten per cent of the males who had urinary difficulties underwent transurethral prostatic resection. Ten grams or less of tissue was removed in two thirds of the cases. The results of operation were very gratifying. No patients were made worse by the operation. Of 13 patients who had urinary incontinence prior to surgical operation, 11 were completely relieved of this condition. There are no clinical data which show that the external vesical sphincter itself is responsible for the difficulty. Emmett and Beare expressed the opinion that obstruction of the vesical neck, however slight, may produce disability among tabetic patients, whereas the same degree of obstruction may not cause any disability among patients who do not have tabes.

*Carcinoma.*—Belt<sup>51</sup> reported on 50 cases in which radical perineal prostatectomy had been done for early carcinoma of the prostate gland. In this group of 50 cases there were 2 postoperative deaths. In 19 of the 50 cases death occurred at a time remote from the time of operation and was caused by metastasis and by local recurrence of the neoplasm. In these 19 cases the extent of the disease was not recognized, because extension beyond the reach of surgical intervention must have occurred prior to the date of operation. Two of the 19 patients lived longer than five years; 2 more lived longer than four years; 2 lived longer than three years; and 4 lived longer than two years. Only 2 of these patients had stoppage of the urine before their death. In a second group, 19 patients were living at the time of Belt's report and exhibited no clinical or laboratory evidence of the existence of

49. Russ, F. H.: Urinary Obstruction and Gastro-Intestinal Symptoms: Report of Two Cases, *Proc. Staff Meet., Mayo Clin.* **17**:257-260 (April 29) 1942.

50. Emmett, J. L., and Beare, J. B.: Bladder Difficulties of Tabetic Patients, with Special Reference to Treatment by Transurethral Resection, *J. A. M. A.* **117**:1930-1934 (Dec. 6) 1941.

51. Belt, E.: Radical Perineal Prostatectomy for Early Carcinoma of the Prostate, *J. Urol.* **48**:287-297 (Sept.) 1942.



cancer. One of these patients had survived for more than fourteen years, another for more than thirteen years, another for longer than ten years, another longer than seven years and still another for longer than six years. Six patients had lived longer than five years; 1 had lived longer than four years and another longer than three years, at the time of Belt's report. Four patients were operated on more than two years prior to the time of Belt's report and 2 were operated on within two years before the time of the report. In the entire group of 50 patients, 10 had died in the years since operation from causes other than cancer of the prostate gland. When the procedure of radical perineal prostatectomy, as described by Belt, is employed, the patient is placed in the extreme lithotomy position. Antiseptic surgical preparation and draping include the fastening of a strip of rubber dam to the patient's skin with clips. This procedure excludes the anus from the surgical field. The curving line of incision is 1.5 cm. from the mucocutaneous juncture. The cut edge of the skin is pulled down, so that the fibers of the median raphe are stretched. These are cut, and the red, circular external rectal sphincter is easily pushed upward, away from the shining, white, longitudinal fibers of the rectum. The levator ani muscles are separated from one another in the midline. They are pushed laterally far enough to reveal the whole posterior aspect of the prostate gland. The vertical fibers of the rectum are depressed below the lower margin of the prostate gland. The lateral aspect of the prostate gland is separated from its bed by blunt dissection. The bundle of vessels which enter it at each lateral inferior border is isolated, ligated and cut between ligatures. A thin, tough veil of fascia which covers the seminal vesicles is incised transversely across the base of the prostate gland, so that the vesicles and ampullae which bulge beneath it are exposed. Seminal vesicles and ampullae are then bluntly dissected from their beds. The large blood vessel which enters each seminal vesicle at its apex is carefully ligated. A long strip of vas is dissected from the retrovesical tissues, to be removed with the specimen. Next, the apex of the prostate gland itself is approached. The gland is cut across, so that a collar of prostatic tissue remains attached to the membranous urethra, where circular muscular fibers encircle the canal. These fibers and the membranous urethra are carefully left undisturbed during the dissection. Dissection is carried forward between the anterior aspect of the prostatic capsule and in the rich plexus of veins which clings to it. The prostate gland now remains attached to the bladder by the mucosa at the neck of the bladder. This tube of mucosa is cut across with scissors, and the prostate gland, with capsule, both seminal vesicles, both ampullae and a long section of each vas, is lifted from the wound. The urethra and neck of the bladder are anastomosed. The urethral catheter is then inserted into the bladder. The tube of mucosa which forms the neck of the bladder and the tube of urethral mucosa formerly situated at the apex of the prostate gland approximate one another around this portion of the urethra. The thin fascial layer which covered the seminal vesicles and was incised transversely over them is now lifted up and stitched to the adventitia, which envelops the membranous urethra; next, the levator ani muscles are brought together with interrupted stitches. The edge of the rectal sphincter is brought into contact with the median raphe by means of a circular stitch. A slender tube of rubber dam is passed down to the posterior aspect of the bladder. The skin is closed with a running subcuticular stitch. The rubber drain is removed within twenty-four hours; the catheter, within seven days.

Ravich<sup>52</sup> discussed the relationship of circumcision to cancer of the prostate gland. He said that in a survey of prostatic operations performed by him from

52. Ravich, A.: The Relationship of Circumcision to Cancer of the Prostate, *J. Urol.* 48:298-299 (Sept.) 1942.

1930 to 1936 at the Jewish, Israel Zion and Beth El hospitals in Brooklyn, and from 1935 to the date of his report at the Adelphi Hospital, on patients whose ethnic status was readily available to him, the following data were obtained: (1) Of the total number of patients who had prostatic obstruction, 768 were Jews and 75 were non-Jews; (2) of the total number who had benign hypertrophy of the prostate gland, 755 were Jews and 60 were non-Jews; (3) of the total number of those who had a malignant process of the prostate gland, 13 were Jews and 15 were non-Jews. The incidence of cancer of the prostate gland among Jews was 1.7 per cent; among non-Jews it was 20 per cent. He expressed the opinion that such a striking difference in the same community is conclusive. Since morphologically Jews and non-Jews are alike, Ravich deduced that the circumcision of male Jews in infancy renders them relatively immune from cancer of the prostate gland in their old age. Cancer of the penis, which is said to occur exclusively among uncircumcised males, is apparently a lymph-borne disease originating from the irritating secretions that accumulate under the foreskin. In cancer of the prostate gland, however, this route may or may not be the one involved. Ravich stated his belief that it is entirely conceivable that the process may have as a basis some parasitic, viral or other carcinogenic agent that infests or involves the urethra and migrates along the lumen of this structure into the prostate gland in somewhat the same manner as that in which gonorrheal prostatitis so often complicates gonorrheal urethritis. Ravich said that another interesting observation had been made by the late Dr. John Osborne Polak, formerly professor of gynecology and obstetrics at the Long Island College of Medicine: that cancer of the cervix was found rarely among his Jewish patients, although it was rather common among non-Jews. This observation recently was substantiated by Frank R. Smith, in a study of cervical carcinoma made in the gynecologic service of a hospital. Such being the case, Ravich considered it conceivable that the disease is transmitted by direct contact to the wives of uncircumcised men during coitus.

Kahle, Ogden and Getzoff<sup>53</sup> reported 7 cases of adenocarcinoma of the prostate gland, in 6 of which the lesion was proved by biopsy. The patients had been treated during the two years prior to the time of this report with diethylstilbestrol or diethylstilbestrol dipropionate. To all the patients treated, this method of therapy brought prompt relief of pain and urinary symptoms and a general improvement in health. Two bedridden patients were restored to activity within four and six weeks, respectively, after the institution of treatment. Clinical improvement was associated in all instances with regression of the malignant lesion. At the time of the patients' last examination all the glands had lost their malignant characteristics, and the authors said it would have been impossible at that time to arrive at a diagnosis of carcinoma on the basis of rectal palpation. Clinical improvement was also associated with regression of metastatic lesions to the bones in the only case in which the making of serial roentgenologic observations was possible, and with regression of metastasis to the lymph nodes in the 2 patients who exhibited such lesions. Reduction in the size and alteration of the consistency of the primary neoplastic lesions, as well as reduction in the metastatic lesions, could be correlated readily with the marked retrogressive tissue changes observed in histologic study of specimens secured for biopsy after treatment.

53. Kahle, P. J.; Ogden, H. D., Jr., and Getzoff, P. L.: The Effect of Diethylstilbestrol and Diethylstilbestrol Dipropionate on Carcinoma of the Prostate Gland: I. Clinical Observations, *J. Urol.* 48:83-98 (July) 1942.

Schenken, Burns and Kahle<sup>54</sup> reported on the results of histologic studies made in 6 cases of carcinoma of the prostate gland in which the patients were treated with diethylstilbestrol or diethylstilbestrol dipropionate. In 5 cases tissue was available for study before and after treatment. In 1 case tissue was not removed before treatment. In all 6 cases treatment was associated with definite regressive changes in the nucleus and cytoplasm of the tumor cells. The ultimate change which may occur in these neoplastic cells is undetermined.

#### TESTICLE, EPIDIDYMIS AND VAS

*Tumors of the Testicle.*—Twinem<sup>55</sup> reported on benign teratoma of the testicle in a boy 3 years old. His parents had noticed that enlargement of the right testicle had been present for two years before Twinem saw the patient. On examination, a painless, nontender, irregular tumor about 4 cm. in size was found in the boy's right scrotal sac. The testicle was removed through a right scrotal incision and found to be involved with a tumorous lesion which contained cartilage. Microscopic examination showed the lesion to be benign. Two years later the patient weighed 41 pounds (19 Kg.) and was in good general condition.

Rosenblatt, Grayzel and Lederer<sup>56</sup> discussed primary malignant tumors of the testicle. These tumors occur most commonly when the patient is between the ages of 20 and 50 years. The average incidence, according to age of the patient, of heterologous tumors shows that they develop earlier than do the homologous neoplasms. Bilateral tumors are rare, and the right side is usually more frequently involved than the left side. In Rosenblatt, Grayzel and Lederer's series, trauma apparently was a factor in 10 per cent of cases. The average duration of symptoms before medical advice was sought was fifteen months. Painless enlargement of the testicle was the most common symptom. The heterologous tumors are accompanied by a more unfavorable prognosis than are the homologous ones.

Wesselhoeft and Vose<sup>57</sup> discussed the surgical treatment of orchitis in mumps. They expressed the opinion that the early surgical treatment of orchitis in mumps accomplishes prompt relief from pain and saves the testicle from subsequent atrophy. In the follow-up examinations of 347 patients not operated on, atrophy was revealed in 190, or 54.7 per cent. Sterility as a result of atrophy is rare. Sterility is not to be confused with impotence, since sterility implies only a lack of sufficient sexual cells. Fear of sterility after the orchitis of mumps sometimes leads to a mental complex that may promote impotence. Twelve patients who had severe orchitis of mumps were operated on. The condition of 9 of these was followed for from six to twelve months after operation, and only 1 of the 9 patients was found to have any observable atrophy of the testicle. Wesselhoeft and Vose stated that the rationale of incision of the tunica albuginea in severe orchitis is somewhat comparable to that of paracentesis of a bulging, painful drumhead in otitis media. The operation must be done sufficiently early to avoid pressure necrosis in the testicle. It is useless to operate when the process is already on the wane. The operation is not indicated when orchitis is mild or when epididymitis predominates. An enlarged, hard,

54. Schenken, J. R.; Burns, E. L., and Kahle, P. J.: The Effect of Diethylstilbestrol and Diethylstilbestrol Dipropionate on Carcinoma of the Prostate Gland: II. Cytologic Changes Following Treatment, *J. Urol.* 48:99-112 (July) 1942.
55. Twinem, F. P.: Benign Teratoma of the Testicle in a Three Year Old Boy: A Case Report, *J. Urol.* 47:577-579 (May) 1942.
56. Rosenblatt, P.; Grayzel, D. M., and Lederer, M.: Primary Malignant Tumors of the Testicle, *Am. J. Surg.* 57:94-103 (July) 1942.
57. Wesselhoeft, C., and Vose, S. N.: Surgical Treatment of Severe Orchitis in Mumps, *New England J. Med.* 227:277-280 (Aug. 20) 1942.

tender testicle, associated with chills and fever, constitutes the indication for surgical intervention. Nitrous oxide and oxygen are the anesthetic agent of choice. An increase in temperature after operation signifies an invasion of some other organ by the virus.

*Epididymitis.*—Lich<sup>58</sup> prepared a local anesthetic agent in oil with nupercaine hydrochloride, which has anesthetizing properties of several days' duration. It induced an insignificant amount of cellular response when it was injected into the subcutaneous tissues of a dog. In a series of 147 cases this anesthetic agent in oil injected into the sheath of the vas promptly stopped the pain of acute epididymitis. The usual treatment for the primary cause of acute epididymitis is essential, since the injection therapy is but a symptomatic measure.

*Tumors of the Spermatic Cord.*—Prince<sup>59</sup> reported a case of angioendothelioma of the spermatic cord. Tumors occurring in the spermatic cord are rare. This case brings the total number of reported cases up to approximately 75. The patient was a man 63 years old who complained of swelling in the scrotum which he had first noticed about fourteen months previously. The testis on this side was found to be in the most dependent part of the sac and was normal except that from its upper pole there arose a firm, nodular, rounded mass 5 cm. in diameter. The testicle and tumor were removed. A diagnosis of "angioendothelioma of the spermatic cord with extension to the connective tissue of the cord at point of its division" was made.

#### PENIS

*Anomaly.*—Cochrane and Saunders<sup>60</sup> reported a case of duplication of the penis with an imperforate anus. Duplication of the penis or diphallus is a very rare anomaly. The baby was normal in every respect except for the genitalia and an imperforate anus. The penis was a well developed but unusual-looking organ with a double glans and a circumference of 3 inches (about 8 cm.) at the shaft. The right glans was the larger. Its length from the meatus to the corona was  $\frac{5}{8}$  inch (1.59 cm.); its circumference, 2 inches (2.5 cm.). The smaller glans was  $\frac{3}{8}$  inch (0.95 cm.) long and its circumference  $1\frac{1}{4}$  inches (about 3 cm.). The scrotum was well developed, and the testes were normal and completely descended. The scrotal circumference was  $5\frac{1}{2}$  inches (about 14 cm.). There was a somewhat redundant prepuce on the left which partly covered the glans on that side. The prepuce on the right was poorly developed. A frenum was demonstrable on both the right and the left side of the glans. Exploration of the urethra was carried out with no. 5 F. ureteral lead catheters. The catheter introduced in the meatus of the left or smaller glans was inserted into the bladder without difficulty. Two drachms (7.5 cc.) of clear amber urine was obtained. The catheter in the right urethra was arrested after it had been passed for 1 inch (2.5 cm.). A roentgenogram made at this stage with the catheters in situ seemed to indicate that the right urethra was blind and that it had no connection with the bladder. It was later observed that while normal urination occurred through the left meatus 4 or 5 drops were passed from the right during the act of micturition. Later the bowel was opened. A month after operation the baby was progressing favorably.

58. Lich, R., Jr.: The Treatment of Acute Epididymitis with Nupercaine in Oil, *J. Urol.* **47**:196-198 (Feb.) 1942.

59. Prince, C. L.: Malignant Tumors of the Spermatic Cord: A Brief Review with Presentation of a Case of Angio-Endothelioma, *J. Urol.* **47**:793-799 (June) 1942.

60. Cochrane, W. J., and Saunders, R. L. de C. H.: A Rare Anomaly of the Penis Associated with Imperforate Anus, *J. Urol.* **47**:818-823 (June) 1942.

McCrea<sup>61</sup> reported a case of congenital absence of the penis. Congenital absence of the penis, like diphallus, is an exceedingly rare anomaly. Only approximately 10 authenticated cases have been previously reported. McCrea's patient was a youth 19 years old. Examination of the genitalia revealed that the penis was totally absent. The scrotum was normally placed. It presented a somewhat bifid contour. The testicles were of normal size; the right one was situated slightly lower than the left one. The distribution of the pubic hair was typically masculine. Results of examination of the perineum revealed nothing abnormal except a small elevation about 1 cm. in front of the anterior anal margin. This elevation was soft and pliable; through this eminence urination was accomplished. The patient had complete urinary control. Rectal examination revealed a prostate gland that was normal in contour and size. However, at the anal margin a distinct tubular structure could be palpated; this structure was considered to be the urethra, since it could be distinctly traced to the eminence on the perineum.

#### URINARY ANTISEPTIC AGENTS

Cook<sup>62</sup> reviewed recent advances in the chemotherapy of infections of the urinary tract. Mandelic acid is effective if the urine contains at least 0.5 per cent of the drug at a  $p_H$  of less than 5.5. Gram-negative bacilli and *Streptococcus faecalis* can be destroyed when these conditions are satisfied. Sulfanilamide, azosulfamide (disodium 4-sulfamidophenyl-2'azo-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate), sulfapyridine and sulfathiazole are effective against the usual gram-negative bacilli and beta hemolytic streptococci. Since sulfonamide compounds are more effective in alkaline mediums, they have been useful in combating organisms which split urea, notably bacilli of the *Proteus* type. Sulfapyridine is of some value in destroying staphylococci and micrococci, but sulfathiazole is the most effective compound in this group. When *Str. faecalis* is present, mandelic acid is the drug of choice. More than 90 per cent of patients who have uncomplicated infections of the urinary tract can be treated effectively with these drugs, provided there is no cicatricial deformity in the kidney, or other complication. Any stone, tumor, foreign body or obstructive formation must be removed before chemotherapy can be used effectively. Likewise, chronic prostatitis must be dealt with by other means if a coexisting infection of the urinary tract is to be relieved by chemotherapy. If the kidney is poorly functioning, azosulfamide can be administered with the least danger, and mandelic acid should not be given. Sulfonamide compounds usually are administered orally in four divided doses amounting to 40 to 60 grains (2.6 to 4 Gm.) daily for periods varying from eight to fourteen days. Close observation of patients receiving sulfonamide compounds is necessary for the detection of any toxic manifestations. If treatment is not effective after two or three courses of chemotherapy, complete urologic study is indicated.

Helmholz<sup>63</sup> found that sulfathiazole is bactericidal for *Escherichia coli* in concentrations lower than those which are bactericidal for any of the other organisms commonly found in the urinary tract, and that sulfathiazole acts therapeutically in doses ranging from 0.75 to 1.0 Gm. (about 12 to 15 grains) per day in an average instance. It is Helmholz' opinion that the administration of sulfa-

61. McCrea, L. E.: Congenital Absence of the Penis, *J. Urol.* **47**:818-823 (June) 1942.

62. Cook, E. N.: Recent Advances with Chemotherapy in the Treatment of Infections of the Urinary Tract, *New England J. Med.* **226**:187-190 (Jan. 29) 1942.

63. Helmholz, H. F., and Larson, N.: Concentration of Sulfathiazole at Which Bactericidal Action Is Lost for Bacteria Commonly Present in Urinary Infections, *Proc. Staff Meet., Mayo Clin.* **16**:404-408 (June 25) 1941.

thiazole in doses of 0.13 Gm. (2 grains) five times a day will prevent the bacterial infections commonly associated with postoperative catheterization. When this dosage is used and when the output of urine is 1,000 cc. per day, it is possible to provide a concentration of the drug in the urine of between 20 and 30 mg. per hundred cubic centimeters.

Helmholz<sup>64</sup> gave directions for the clinical administration of methenamine, mandelic acid, sulfanilamide and sulfathiazole as indicated by recent developments in chemotherapy in the treatment of infections of the urinary tract. In the presence of badly damaged kidneys, sulfathiazole in doses of as little as 1 grain (0.065 Gm.) a day has brought about striking effects in the appearance of the urine. Because of the inhibitory effect of small doses of sulfathiazole on nearly all types of organisms, with the notable exception of *Str. faecalis*, Helmholz suggested that this compound be used as a prophylactic agent against postoperative infections of the urinary tract. He pointed out that sulfathiazole may be effective against *Str. faecalis* at concentrations of less than 30 mg. per hundred cubic centimeters of urine, provided the  $p_H$  is 5.5 or less.

Strom and Thompson<sup>65</sup> administered sulfathiazole prophylactically to 100 consecutive patients who had undergone transurethral prostatic resection, and compared the clinical response of the patients to the response of a similar number of patients who did not receive sulfathiazole. Sulfathiazole administered prophylactically ( $7\frac{1}{2}$  grains or 0.48 Gm.) four times daily was found to lessen the postoperative febrile reaction and the number of complications. The authors urge caution in the use of sulfathiazole among elderly patients because of the potential danger of toxic reactions.

Rettino and La Rotonda<sup>66</sup> reported a case in which death followed the administration of sulfadiazine for pneumonia. A total of 61 Gm. of sulfadiazine was administered during a period of eleven days, but a value for the drug in the blood of 20.7 and 23 mg. per hundred cubic centimeters was maintained. After this the patient complained of dysuria, and the urine contained erythrocytes and sulfadiazine crystals. On the first examination the urine had been clear. The patient died rather suddenly after two days of abdominal distention. Both kidneys were found to be large and congested, and the microscopic examination disclosed numerous crystals. Study of the kidneys disclosed changes in the excretory and secretory tubules and glomeruli. Most excretory tubules were dilated, some to such an extent that they had herniated and ruptured through the perirenal capsule covering the hilar surface of the kidney. Within their lumens was found a variety of substances: polymorphonuclear leukocytes, coagula and crystals. Polymorphonuclear leukocytes were found in large numbers in some tubules. Crystals were best demonstrated in sections prepared by frozen section. They appeared large and fan shaped. Glomeruli were numerous and large. Many were ischemic, although their capillaries appeared to be widely dilated. Epithelial and endothelial cells seemed well preserved, swollen but not hyperplastic. An occasional glomerular capillary was adherent to Bowman's capsule.

64. Helmholz, H. F.: Recent Developments in the Treatment of Urinary Infections, *Southwestern Med.* 25:286-289 (Sept.) 1941.

65. Strom, G. W., and Thompson, G. J.: The Effect of Sulfathiazole on Febrile Reactions Following Transurethral Prostatic Resection, *Proc. Staff Meet., Mayo Clin.* 17:241-256 (April 22) 1942.

66. Rettino, A., and La Rotonda, O.: A Fatal Human Case of Urolithiasis Medicamentosa Caused by Sulfadiazine, *J. Urol.* 48:310-317 (Sept.) 1942.

Greene, Pool and Cook<sup>67</sup> treated 42 patients who had various types of infection of the urinary tract with sulfadiazine, in divided doses of 3 Gm. or less administered daily. *Esch. coli* and micrococci were the most common organisms, although others were encountered. In 24 cases (57 per cent) the urine was rendered sterile and in 12 cases (29 per cent) improvement was noted. Complete failures occurred in 6 cases (14 per cent). In a few cases, sulfadiazine was found to be as effective as sulfathiazole in the treatment of gonorrhea. In conclusion, they stated that sulfadiazine is slightly less effective and more expensive, but less toxic, than sulfathiazole.

Bandler and Bruger<sup>68</sup> discussed suppression of urination caused by sulfathiazole. The most common complications are hematuria, oliguria and anuria, renal insufficiency, and precipitation of crystals in the tubules, renal pelvis, ureters and bladder. They reported a case in which suppression of urination and retention uremia were caused by sulfathiazole, with recovery of the patient achieved by ureteral manipulation, pelvic lavage and an increased intake of fluids.

#### UROGRAPHY

Findley, Edwards, Clinton and White<sup>69</sup> stated that intravenous urography can be converted into a satisfactory test of renal function by determination of the quantity of iodine which appears in the urine under standard conditions. Normal persons excrete approximately 45 per cent of the injected dose of 3,5-diiodo-4-pyridone-*N*-acetic acid and diethanolamine (diodrast) or a compound of this contrast medium in thirty minutes, and reductions in the rates of excretion of iodine are roughly proportional to variations in the clearance of urea.

#### ANESTHESIA

Nesbit<sup>70</sup> stated that the ideal anesthetic agent for urologic instrumentation should fulfil several requirements. It should relieve apprehension, which causes the patient to exaggerate all painful stimuli. It should also effectively prevent pain. Stimuli from reaching the higher centers and should blot out the memory of pain. It should be a short-acting agent to facilitate full postcystoscopic cooperation of the patient and should not produce nausea or other unpleasant sequelae which might be as objectionable as the averted pain. Furthermore, the ideal anesthetic agent should have a wide margin of safety and be inexpensive and easily administered. A new field for clinical investigation has been opened by the advent of intravenous anesthetic agents. Anesthesia produced with pentothal sodium has been used for three years and fulfils most of the requirements that have been enumerated. In an effort to utilize the distinct advantages of anesthesia with pentothal sodium and to eliminate the disadvantages of that agent, Nesbit devised a technic of administration of it for urologic instrumentation which has proved so satisfactory as to approach the requirements that have been set up for the ideal anesthetic agent. The actual technic of administration is as follows: Preoperative medication, consisting of the hypodermic injection of  $\frac{1}{6}$  grain (0.01 Gm.) of morphine sulfate, is administered to the patient on call. The patient is prepared for cystoscopic examination in the usual manner and a small bore needle is

67. Greene, L. F.; Pool, T. L., and Cook, E. N.: Sulfadiazine in the Treatment of Infections of the Urinary Tract, *Proc. Staff Meet., Mayo Clin.* **17**:497-512 (Sept. 23) 1942.
68. Bandler, C. G., and Bruger, M.: Urinary Suppression Due to Sulfathiazole, *New York State J. Med.* **42**:1627-1630 (Sept. 1) 1942.
69. Findley, T.; Edwards, J. C.; Clinton, E., and White, H. L.: Intravenous Urography: A Test of Renal Function, *J. Urol.* **48**:119-125 (July) 1942.
70. Nesbit, R. M.: Pentothal Analgesia, *J. Urol.* **47**:738-740 (May) 1942.

introduced into the vein in the arm. Administration of a 2.5 per cent solution of pentothal sodium is then begun; the solution is administered slowly. Usually, the patient states that he is sleepy after from 6 to 10 cc. of the anesthetic agent has been administered. When the patient says he is very sleepy, the examining physician replies: "I am now going to pass an instrument which you will feel. It will not hurt you. You are to remain quiet and relaxed while I am carrying out this examination." So saying, the examining physician passes the instrument and conducts the examination. The anesthetist continues to administer small amounts of the anesthetic agent as required during the examination in order to keep the patient entirely cooperative. At the end of the examination, when instruments have been removed, administration of the anesthetic agent is stopped and within a few seconds' time the patient is conscious and entirely willing and able to cooperate with any instruction which is given.

#### TUBERCULOUS BACILLURIA

Ordway and Medlar<sup>71</sup> discussed tuberculous bacilluria. They accumulated data over a ten year period on the presence of *Mycobacterium tuberculosis* in the urine of clinically tuberculous and nontuberculous patients. Results of a total of 1,074 inoculations of guinea pigs, with sediments from twenty-four hour specimens of urine obtained from 287 tuberculous patients and 112 nontuberculous patients, have been recorded. Of the tuberculous patients, 22 (7.7 per cent) had urine which contained *Myco. tuberculosis*. Of these, 17 (77 per cent) had no clinical symptoms suggestive of renal tuberculosis. Leukocytes and erythrocytes in urinary sediment do not necessarily indicate the presence of *Myco. tuberculosis*. The presence of this organism in the urine does not indicate that progressive renal tuberculosis will inevitably follow. Surgical intervention should therefore be delayed until such a time as progressive renal destruction has been proved.

*Myco. tuberculosis* is not commonly found in the urine, even in cases of far advanced pulmonary tuberculosis, and can be demonstrated repeatedly in some cases in which tuberculous infection has not been suspected.

#### HEMATURIA

Cahill<sup>72</sup> presented a review of the various diagnoses arrived at in a urologic service and the occurrence of hematuria as a symptom among the conditions diagnosed. Cahill's figures show that hematuria is a serious symptom, and that in the majority of cases it is associated with some serious lesion, such as tumor, infection or calculus. A study of 89 cases in which the cause of hematuria was not apparent after a first investigation indicated that sooner or later reinvestigation showed a cause for the hematuria to be present in 55 of these cases. There is also a group of cases of so-called essential hematuria in which various pathologic lesions will be found or no pathologic lesions at all will be found.

#### URINARY CONCRETION

Posey<sup>73</sup> described certain lesions of the renal papillae resembling the calcium infarct. These lesions were found in 66 instances in 340 consecutive necropsies, exclusive of infants less than 3 weeks of age, stillborn babies and subjects on whom only partial necropsy had been carried out. In 39, or 59 per cent, of the cases

71. Ordway, W. H., and Medlar, E. M.: Tuberculous Bacilluria: A Ten Year Study, *J. A. M. A.* **119**:937-942 (July 18) 1942.

72. Cahill, G. F.: Hematuria: Its Clinical Significance, *J. Urol.* **47**:224-234 (March) 1942.

73. Posey, L. C.: Urinary Concretions: II. A Study of the Primary Calculous Lesions, *J. Urol.* **48**:300-309 (Sept.) 1942.



in which papillary lesions were present there were grossly recognizable stones and in only 6 of these cases had the patient ever had symptoms of calculous disease. The papillary lesion was observed in renal pyramids when phosphate, oxalate or urate stones were present. The papillary lesions probably precede actual clinical calculous disease, and other factors, such as stasis, infection and avitaminosis, may contribute to the development of calculi so formed. The condition appears to be primary vascular degeneration, which is probably different from ordinary atherosclerosis, since it may be present in the absence of recognizable atherosclerosis. It is suggested that the vascular degeneration seen in the primary calculous lesion of the renal papilla may be related to hyperexcretion of an insoluble urinary salt.

Balch<sup>74</sup> stated that the development of urinary calculi during pregnancy is rare, only 3 instances of such calculi being found in 36,101 deliveries. Three cases are reported; in 2 the calculi were renal and in 1 they were ureteral. The most likely reason for such a low incidence is pelvic and ureteral dilatation, which allows free passage of any formations of crystals. Ureteral atony which occurs during pregnancy no doubt is the reason for the fact that ureteral colic is so rare. Renal and ureteral operations seldom cause miscarriages, nor do they cause a greater mortality rate among gravid women than they do among nongravid women. Pregnancy at any stage does not increase the technical difficulties of removal of stones in the kidney or upper half of the ureter, but it is practically impossible to carry out surgical treatment of the lower part of the ureter during the last trimester. Cystoscopic manipulation of ureteral calculi during pregnancy is not recommended, except in selected cases.

*Tests for Concentration of Urine.*—Kottke, Code and Wood<sup>75</sup> undertook to determine the power of the kidney to do its work in general and its ability to excrete excess chloride in the absence of the adrenal cortical hormone, but with the animal in good condition and maintained on a diet high in sodium and low in potassium. Dilution of the urine and tests of concentration and a test of renal chloride concentration were carried out on dogs before and after adrenalectomy. Results of their experiments indicate that the ability of the kidney of the adrenalectomized dog to dilute urine, that is, to reabsorb the crystalloids and leave the water of the glomerular filtrate, is not impaired by the operation. On the other hand, results of tests of concentration indicate that the power of adrenalectomized dogs, maintained on a diet high in sodium and low in potassium without cortical hormone, to concentrate urine, that is, to reabsorb water selectively, is reduced even when these animals are in excellent general condition.

In the performance of tests of the concentration of chloride, it was found that there is a tendency for the rate of production of urine in the adrenalectomized animals to increase slowly to a maximum and to remain fixed at this level throughout the test. This fixed rate of production of urine, as a rule, was less than the maximal rate of production of urine observed in intact animals. The maximal concentration of chloride was limited in the adrenalectomized animals to less than 11.6 Gm. per liter of urine, whereas in the intact animals the concentration increased to considerably higher values. Likewise, the maximal output of chloride per minute was always less in the adrenalectomized animals than in intact animals. These results would indicate some reduction in the power of the tubular function of the kidney which is amply supplied with sodium chloride but which is deprived of cortical hormone to concentrate chloride in the urine.

74. Balch, J. F.: Urinary Calculus Associated with Pregnancy: A Consideration of Management with Report of Three Cases, *J. Urol.* **47**:705-710 (May) 1942.

75. Kottke, F. J.; Code, C. F., and Wood, E. H.: Urine Dilution and Concentration Tests in Adrenalectomized Dogs, *Am. J. Physiol.* **136**:229-243 (April) 1942.

*The Production of Diuresis.*—To determine the effect on the renal tubules of the repeated intravenous injection of an 8 per cent solution of sucrose in half-strength Ringer's solution as a measure to produce diuresis, Helmholz and Bollman<sup>76</sup> used 7 rabbits and 4 dogs in their experiments. In both species the most striking changes in the urine or urinary system, as well as in the values for phenolsulfonphthalein and urea, were noted after the first injection. These changes were temporary, and repeated injections produced neither the same acute changes nor any permanent damage in the histologic structure or the function of the kidney. Although the tubular epithelium seemed to be considerably changed histologically after the injection of this solution, it seemed able to function. The appearance of casts, albumin and sometimes erythrocytes in the urine was likewise temporary. Rabbits can excrete from 90 to 100 per cent of fluid when it is given in the form of an 8 per cent solution of sucrose in half-strength Ringer's solution at a rate of 100 cc. per kilogram of body weight per hour for a six hour period. Such injections can be repeated as often as every other day. Dogs can excrete 80 per cent of the fluid when it is given at a rate of 50 cc. per kilogram of body weight per hour for a six hour period weekly. In neither animal do the kidneys exhibit any permanent damage after multiple injections of the solution, and they regain their normal histologic structure within ten days. Helmholz and Bollman concluded that this solution can be used justifiably in clinical emergency conditions in which the rapid production of diuresis is desired.

#### ENDOCRINE THERAPY

Kearns<sup>77</sup> stated that pellet implantation offers a desirable and safe means for the administration of testosterone to patients who are dependent on testosterone replacement therapy or who are greatly inconvenienced by visits to the physician's office, because of either their remote location or their hours of work. Apparently there are no objections to this form of treatment. In a considerable number of cases (approximately 85 in which such implantation has been carried out during the past two years) no untoward effect has been observed, and it was Kearns's belief that it is a safe procedure.

#### HERMAPHRODITISM

Chanis<sup>78</sup> discussed some aspects of hermaphroditism and reported a case of female pseudohermaphroditism. The patient was a Negro 18 years old. At birth, the attending physician had declared the patient to be a male. From the age of 12 years onward the patient had had occasional penile erections. At 14 years of age small amounts of blood had been passed in the urine monthly. At 16 years the patient apparently was sexually a normal male. Urination and evacuation of semen had been accomplished through an orifice in the scrotum. Physical examination disclosed a normal penis except that the urinary meatus ended blindly in a pouch 3 cm. long. There was a small opening in the base of the scrotal raphe, through which the urine was voided. Testicles could not be palpated. The mammary glands were well developed. Surgical exploration of the abdomen disclosed a small uterus with two tubes, and two well developed ovaries were seen. Testicles were not found. Subtotal hysterectomy was done, and later a plastic operation on the breasts was carried out. A follow-up report secured a year later indicated that the condition of the patient apparently was more satisfactory than before.

76. Helmholz, H. F., and Bollman, J. L.: Intravenous Use of Sucrose-Ringer's Solution to Produce Maximal Diuresis, *J. Lab. & Clin. Med.* **27**:606-615 (Feb.) 1942.

77. Kearns, W. M.: Pellet Implantation of Hormones in Urology, *J. Urol.* **47**:587-590 (May) 1942.

78. Chanis, D., Jr.: Some Aspects of Hermaphroditism: Report of a Case of Female Pseudohermaphroditism, *J. Urol.* **47**:508-514 (April) 1942.

## News and Comment

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**American Urological Association.**—A meeting of the American Urological Association will not be held this year, in view of the fact that the government is discouraging the holding of all conventions except those primarily of military interest. The \$500 research prize which is offered annually by the association will therefore not be awarded this year.

**Meeting of International College of Surgeons.**—The Fourth International Assembly of the International College of Surgeons will be held June 14 to 16 at the Waldorf Astoria Hotel, New York. Dr. Fred H. Albee, of New York, is the international president, and Dr. Max Thorek, of Chicago, the international executive secretary. Dr. Manuel A. Manzanilla, of Mexico, and Prof. Herman de las Casas, dean of the University of Caracas, Venezuela, will serve as chairmen of the program coordination for Central and South America, and Dr. Rudolph Nissen, of New York, will act for Europe. The rehabilitation committee is composed of Drs. Fred H. Albee (New York), William D. Ryan (Detroit) and Custus Lee Hall (Washington, D. C.). Dr. A. A. Berg (New York) is chairman of the program committee; Dr. Charles Phillips (New York), chairman of the arrangements committee; Dr. Chester A. Peake (Brooklyn), chairman of the exhibit committee, and Dr. Milton Bodenheimer (New York), chairman of the publicity committee.

**Examination by American Orthoptic Council.**—The next examination by the American Orthoptic Council will be held in September and October 1943.

The written examinations will be held at various cities in the country on September 9. Only those passing the written examinations will be permitted to take the oral and practical tests, which will be given in Chicago on October 9.

Applications on official forms should be addressed to the American Orthoptic Council, 23 East Seventy-Ninth Street, New York, for receipt before Aug. 1, 1943.

**Reprints of "Progress in Orthopedic Surgery" Available.**—Arrangements have been made whereby reprints of "Progress in Orthopedic Surgery for 1941," which appeared in the September, October, November and December 1942 and January 1943 issues of the ARCHIVES OF SURGERY, may be procured at \$1 a copy. Checks should be made payable to Dr. A. R. Shands Jr. and sent to 535 North Dearborn Street, Chicago.

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### CORRECTION

In the article by Drs. Davis, Frank, Hurwitz and Seligman entitled "Intravenous Use of Vitamin K<sub>1</sub> Oxide," in the February issue (ARCH. SURG. 46:296, 1943), figures 2 and 3 (not the legends) are reversed.

## EFFECTS OF JEJUNAL TRANSPLANTS ON EXPERIMENTAL PRODUCTION OF PEPTIC ULCERS

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AND

PAUL STEFKO

NEW YORK

Stefko, Andrus and Lord<sup>1</sup> recently described the effects on the gastric secretion of transplantation to the stomach of a segment of jejunum with intact blood supply. Briefly, they observed that in 5 animals subjected to this procedure the normal response of increased acidity after injection of histamine was reversed in 4 and markedly reduced in the fifth, as demonstrated by direct measurements of the  $p_{H}$  of the gastric mucosa of seven regions of the stomach. This same reversal was also strikingly evident in the analyses of the gastric contents, which showed a reduction of the average fasting free and combined acidities after jejunal transplantation, followed by a still further decrease after the injection of histamine.

The present paper deals with the effects of such jejunal transplants on experimental production of peptic ulcers of the duodenum through daily intramuscular injection of a mixture of histamine phosphate and beeswax in liquid petrolatum as reported by Varco and his associates.<sup>2</sup> These authors attributed such ulcers to "the continuous excessive secretion of acid gastric juice evoked by the histamine in the beeswax mixture." In view of the effects of the jejunal transplants in normal animals when the usual amount of histamine phosphate (1 mg.) was injected for gastric analysis, it was felt desirable to investigate the effects during more prolonged exposure to the drug. To this end two series of experiments were carried out.

### EXPERIMENTS

In the first series, 2 control dogs and 2 dogs in which a jejunal segment with intact blood supply had been implanted into the stomach about two and a half months previously received intramuscular injections of a mixture of histamine and beeswax equivalent to 120 mg. of histamine phosphate daily, except for Sunday, for a period of thirty days. At the end of the thirty day period gastric analyses

This study was carried out under a grant from the John and Mary R. Markle Foundation.

From the Department of Surgery of the New York Hospital and Cornell University Medical College.

1. Stefko, P.; Andrus, W. DeW., and Lord, J. W., Jr.: Effects of Jejunal Transplants on Gastric Acidity, *Science* 96:208 (Aug. 28) 1942.

2. These authors (Varco, R. L.; Code, L. F.; Walpole, S. H., and Wangenstein, O. H.: Duodenal Ulcer Formation in the Dog by Intramuscular Injections of a Histamine Beeswax Mixture, *Am. J. Physiol.* 133:P475 [June] 1941) described the preparation as follows: "The histamine beeswax mixture was prepared by mixing finely ground histamine with one part hot beeswax and then diluting with four to five parts hot mineral oil. When homogeneous and while still molten, the mixture was drawn into a 1 cc. tuberculin syringe and allowed to solidify at room temperature."

were carried out, after which all 4 were killed and the gastrointestinal tract carefully examined. Results of gastric analyses performed at the end of the experimental period for these 4 animals appear in the accompanying table.

*Results of Gastric Analyses of Animals in First Series*

		Fasting	10 Minutes After Injection	20 Minutes After Injection
Dog 1 (transplant)	Free.....	30	28	18
	Combined.....	30	21	22
	Total.....	60	52	40
Dog 2 (transplant)	Free.....	50	40	0
	Combined.....	38	22	25
	Total.....	88	72	25
Dog 3 (control)	Free.....	70	70	102
	Combined.....	40	50	40
	Total.....	110	120	142
Dog 4 (control)	Free.....	70	74	90
	Combined.....	38	40	30
	Total.....	108	114	120

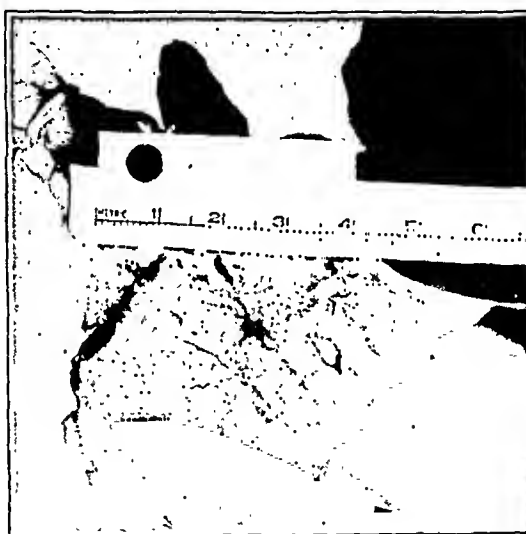


Fig. 1.—Erosion, 11 by 6 mm., in the first portion of the duodenum of dog 3.

Several facts are to be noted. First, the fasting free acidity was much lower in the experimental than in the control animals despite the prolonged exposure to histamine. Also, the previously noted reversal of the normal response of increased acidity ten and twenty minutes after injection of histamine was seen in these animals.

The observations at autopsy were as follows: Dog 3 had multiple erosions, both small and large (diameter of 4 to 11 mm.), in the first and second parts of the duodenum. Some of the erosions had penetrated to the submucosa, and the surrounding mucosa was hyperemic. The stomach was entirely normal (fig. 1). Dog 4 had multiple superficial punctate erosions in the first and second portions of the duodenum, and the mucosa of the pylorus and duodenum was hyperemic. Otherwise the organs of the animal were entirely normal.

On the other hand, careful examination of the duodenum and the remainder of the gastrointestinal tract of the 2 dogs with jejunal transplants failed to reveal any pathologic abnormality. The jejunal transplant in each dog had healed well and appeared unremarkable.

While the results in the first series of animals appeared highly suggestive so far as the action of a jejunal transplant in preventing duodenal ulceration following

prolonged exposure to histamine was concerned, it seemed desirable to pursue the matter further and, if possible, observe the effect of the operation in the presence of duodenal ulceration. A second series of animals was therefore investigated, consisting of 6 normal dogs and 1 with a jejunal transplant in the stomach. All were given injections of the mixture of histamine and beeswax equivalent to 120

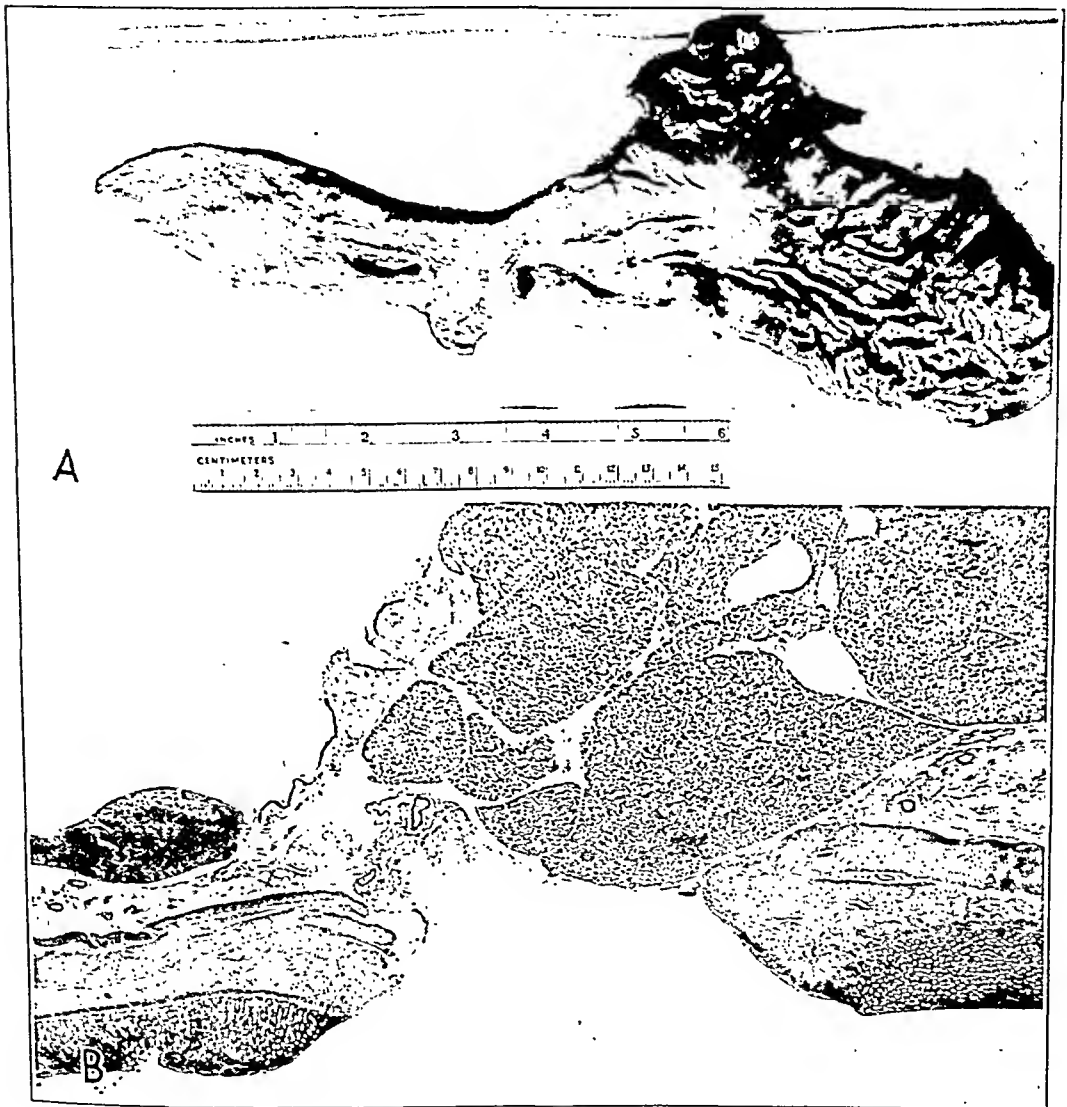


Fig. 2.—*A*, part of the stomach and duodenum of dog 5, showing two large penetrating ulcers in the first and second portions of the duodenum and several erosions through the mucosa of the antrum. *B*, low power photomicrograph of a cross section of the ulcer in the second portion of the duodenum. Complete destruction of the entire wall of the duodenum has occurred, with the pancreas forming the greater portion of the base of the ulcer. Two good-sized vessels can be seen in the base of the ulcer.

mg. of histamine phosphate daily for a period of seven weeks. The animal with the jejunal transplant was observed for the entire period and was then killed while in a state of good health. The others were examined at various times during the experiment when they appeared ill.

In all 6 of the previously normal animals hyperemia and lesions of the duodenal mucosa developed at some time during the experimental period. In 3 definite duodenal ulcerations extending into the muscularis were found, while in the remainder multiple mucosal erosions were to be seen. All suffered from anorexia and lost weight, and several had definitely tarry stools.

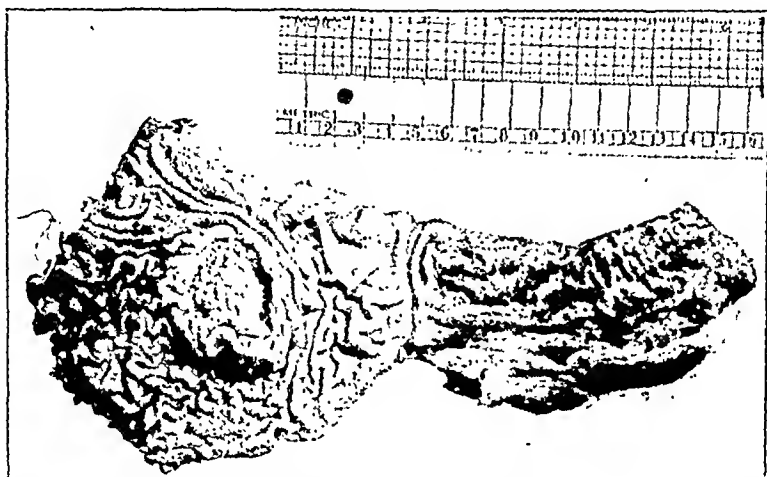


Fig. 3.—Part of the stomach and duodenum of dog 6. The jejunal transplant can be seen in the center of the stomach. The mucosa of the stomach and duodenum is entirely free from erosions and ulcers.

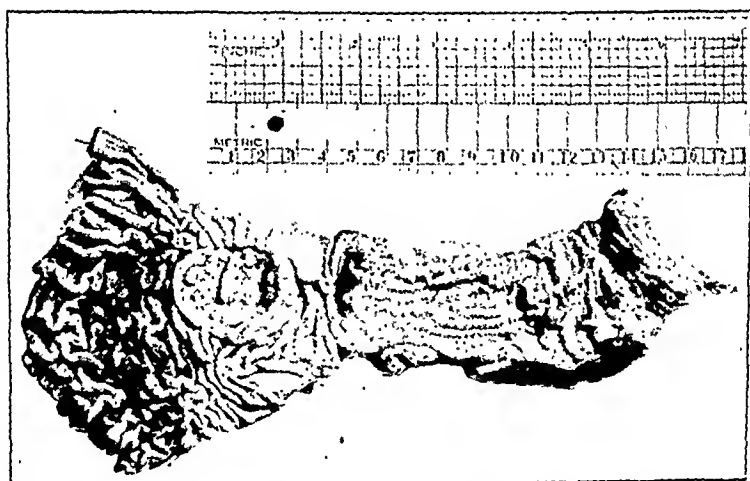


Fig. 4.—Part of the stomach and duodenum of dog 7, showing normal mucosal lining. The jejunal transplant can be seen near the pylorus.

The course of dog 5 was typical of that in the 3 control dogs in which ulcers developed during the experiment. This dog began to lose appetite and weight on the ninth day after the injections of the mixture of histamine and beeswax were begun (July 6, 1942) and continued to do poorly for two weeks, when it began to improve, ate all of its food and put on weight. On August 5 the routine was changed slightly, the injection of the mixture being made in the late afternoon instead of in the morning when the dogs were fed. The next day the dog began to vomit its food. During the next four days it went rapidly downhill, refusing

to eat and vomiting, and finally it began wheezing and died on the thirty-fifth day of the experiment, five days after the change in the time of the injection of the mixture. The animal lost 8 pounds (3.6 Kg.) in weight during the entire period of thirty-five days. Autopsy showed two large, deep ulcers in the first and second parts of the duodenum. Also, there were multiple erosions of the mucosa of the stomach and duodenum associated with hyperemia (fig. 2). Several ounces of bloody fluid was in the stomach. Both lungs were the seat of a bronchopneumonia of a moderate degree.

In contrast, the dog with the jejunal transplant (dog 6) tolerated the prolonged exposure to histamine extremely well, remaining in excellent health throughout the experiment. At autopsy its stomach and duodenum appeared entirely normal (fig. 3).

Two animals were operated on while acutely ill, with the idea of establishing the presence of duodenal ulceration by direct examination and then, after implanting a segment of jejunum in the stomach, observing its effect during continued exposure to histamine. One of these animals died twenty-four hours later with confluent bronchopneumonia, but the other recovered promptly from the operation. This animal, dog 7, had become ill shortly after the onset of the experiment. Tarry stools were noted on the eighth day, and anorexia became complete during the next four days, associated with a moderate decrease in weight (from 26 to 24 pounds [11.8 to 10.9 Kg.]). On the twelfth day a duodenotomy and a jejunal transplant to the stomach were carried out. Several punctate erosions of the duodenal mucosa were seen. The stomach contained some gastric juice, which on testing showed free acidity of 80 degrees and combined acidity of 50 degrees, a total of 130 degrees. No frank ulcer could be palpated or seen through the duodenotomy incision or the window in the anterior wall of the antrum prior to the implantation of the jejunal segment. Postoperatively, the daily injection of the mixture of histamine and beeswax was continued for the remaining twenty-six days of the experiment. No food or water was administered for forty-eight hours, infusions of dextrose and saline solution having been given on the operative day and for the next two days. On the third postoperative day the dog was allowed water by mouth, and shortly thereafter it was given milk and bread. For the last two weeks of the experiment the animal was fed only chopped meat. Immediately postoperatively its condition improved, and it ate everything given it without incident for the duration of the experiment and gained 4 pounds (1.8 Kg.) in weight. A gastric analysis on the tenth postoperative day showed the following values:

	Fasting	10 Minutes After Injection	20 Minutes After Injection
Free acid.....	34	32	20
Combined acid.....	28	28	24
Total.....	62	60	44

The animal was killed on the twenty-sixth postoperative day, and at autopsy the mucosa of the stomach and duodenum was entirely normal. The transplant had healed cleanly, and its mucosa was intact. The duodenotomy incision had been closed satisfactorily without narrowing the lumen (fig. 4).

#### SUMMARY

The previous observation<sup>1</sup> that dogs with pedicle grafts of jejunum transplanted into the stomach wall secrete a gastric juice which becomes relatively more alkaline in response to histamine, in contrast to the normal reaction, has been confirmed in animals given larger doses of the drug for a relatively long period.



The results suggest efficacy of such transplants in preventing development of duodenal erosions and ulceration during continued exposure to histamine.

In the single animal in which it could be satisfactorily carried out, implantation of a pedicle graft of jejunum into the gastric wall was followed by healing of the duodenal lesions despite continuation of the injections of histamine.

The clinical application of transplantation of a jejunal segment with intact blood supply to the stomach in the treatment of peptic ulcer is suggested by these results. Further experimental work is in progress in an attempt to elucidate the mode of action of such a transplant and to establish its possible limitations. Such grafts have been shown<sup>3</sup> to remain viable for long periods, provided their blood supply is intact, and we have observed animals in which the operation has been performed up to two and a half years before, during which time they have remained in excellent health despite other operative procedures.

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3. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, *Arch. Surg.* 8:791 (May) 1924.

# HEMANGIOMA OF JOINTS

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In 1939 Dr. George Bennett and I<sup>1</sup> reviewed the 24 reported cases of hemangioma of the knee joint, and in adding 5 more proposed the use of roentgen therapy for tumors of the nonpedunculated type. Attempts at radical excision had proved unsatisfactory for this type of hemangioma.

The purpose of this paper is to present 4 more cases of hemangioma of the knee joint and to bring out the fact that this tumor is not so rare that it should not be considered as a possibility in any differential diagnosis of swelling of the knee joint. Too often the diagnosis of early tuberculosis of the synovial membrane of the joint or of some minor injury to the joint is made. In many instances the cardinal signs of a family history of hemangioma, hemangiomas elsewhere on the patient's body, intermittent attacks of swelling and reduction of the size of the swelling of the knee on elevation of the extremity will make the diagnosis clear.

In 1 of the following 4 cases the patient was treated by excision of a pedunculated tumor. Roentgen therapy was employed in the other 3 after the diagnosis had been established by biopsy and the lesion had been found to be too extensive for surgical excision.

## REPORT OF CASES

### CASE 1.—*Synovial Hemangioma.*

V. K., an 11 year old girl, was admitted to the Children's Hospital Orthopedic Dispensary, Washington, D. C., in December 1939 because of a swollen right knee of several months' duration. No other symptoms or signs were noted at the time of admission. The condition was diagnosed as a possible epiphysitis of the tibial tubercle, and a cast was applied. After three months in the cast the joint was still swollen. Aspiration was done, and guinea pigs were inoculated with the fluid obtained. The fluid was not blood, and laboratory tests gave negative results. The second cast was removed after two months, and physical therapy was instituted. The swelling of the joint persisted, although at certain times it was more swollen than at others. Ten months after the patient's first visit to the clinic a biopsy of the synovial membrane of the joint was performed, and the lesion proved to be a hemangioma. Roentgen therapy was started, and four months later the knee was apparently entirely well. The results of a careful two year follow-up indicate that it has remained so.

### CASE 2.—*Pedunculated Tumor.*

R. H., a Negro woman aged 23, was first seen at the Garfield Hospital, Washington, D. C., on Feb. 20, 1941, and gave a history of having had pain and stiffness in her left knee for a period of a year. About three weeks before the onset of the pain the patient had fallen, but she could not recall injuring the knee at that time and had no pain in it afterward. She noticed that the pain and swelling had been definitely intermittent in type. At times they were so severe she was unable to extend the leg fully. There was no family history of hemangioma, and none was found on the patient at physical examination. The first examination revealed definite swelling and slight increase in synovial fluid but no definite capsular thickening. Except for generalized obesity there were no other physical signs. Roentgen

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1. Bennett, G. E., and Cobey, M. C.: Hemangioma of Joints, Arch. Surg. 28:487-500 (March) 1939.

examination gave negative results. The preoperative diagnosis was tumor of the left knee. At operation a pedunculated hemangioma was found extending from the synovial membrane posteriorly between the cruciate ligaments out into the anterior portion of the joint. The pedicle was ligated, and the tumor was excised. The patient was given physical therapy postoperatively from March 11 to May 22. She was followed closely for one year after the termination of treatment and at the time of the last examination was apparently entirely well.

*CASE 3.—Synovial Tumor; Hemangioma in Other Members of the Family.*

B. M., a white girl aged 4 years, was brought to my office on May 15, 1941, with the complaint of swelling of the right knee and limping for six weeks. The joint was swollen throughout and felt doughy on palpation. There was a definite decrease in the amount of swelling of the joint on elevation of the extremity. On the left leg there was an extensive

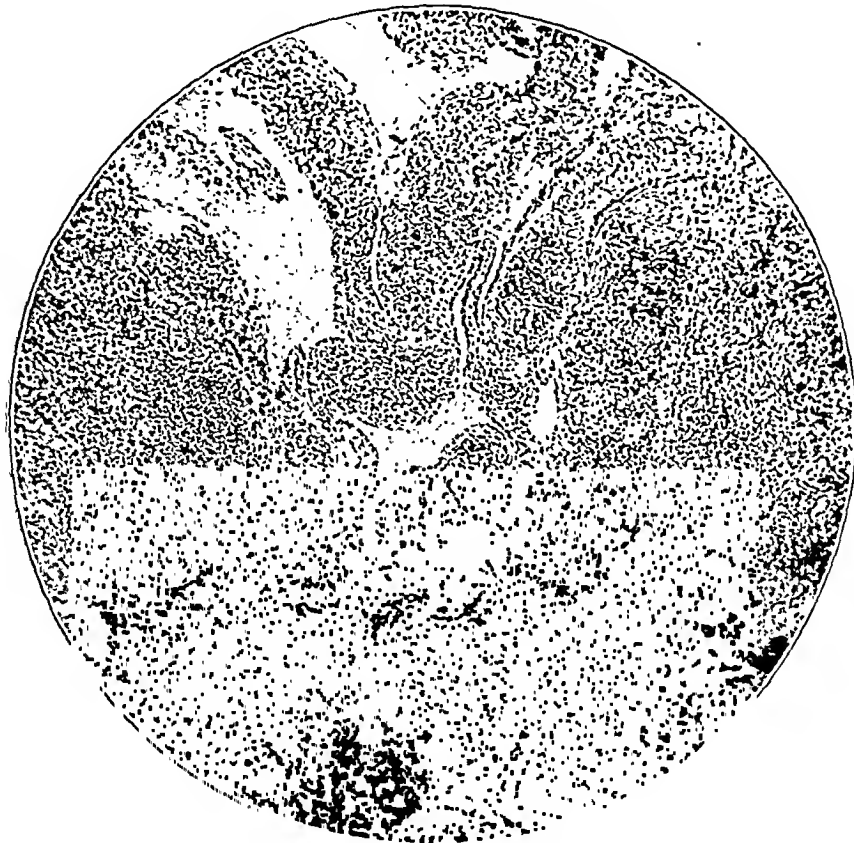


Fig. 1 (case 3).—Low power photomicrograph showing a section from a hemangioma of the knee joint.

bluish discoloration of the skin from dilated subcutaneous vessels. The patient's younger sister had a hemangioma of the face; a paternal aunt had an extensive hemangioma of the deltoid muscle, and a paternal first cousin had a very large hemangioma of the scalp. Roentgen examination of the patient's knee showed numerous small phleboliths in the vessels of the capsule of the joint. Biopsy showed the tumor mass involving the capsule of the joint and the synovial membrane to be a hemangioendothelioma. The patient was not given roentgen therapy until one year after the diagnosis was made, because the parents at first refused to permit treatment. She then had a full course which resulted in prompt improvement. Examination one year after roentgen therapy showed the knee to be apparently entirely well.

*CASE 4.—Synovial Tumor Erroneously Diagnosed as Tuberculosis and Treated with Cast for Eight Years.*

I. S., a white girl aged 10 years, was admitted to the Orthopedic Dispensary of the Children's Hospital, Washington, D. C., on March 24, 1942, with a history of intermittent pain

and swelling in the right knee with a limp on walking since she was 18 months of age. She had spent most of the intervening time in casts and had been in and out of several tuberculosis sanatoriums, being treated for supposed tuberculosis of the knee joint. On examination there was 1.5 cm. overgrowth in length of the right leg and some atrophy of the muscle of the thigh. The capsule of the joint was definitely thickened on palpation, and the swelling decreased on elevation of the extremity and increased when it was placed in a dependent position. Examination of tissue removed for biopsy indicated the presence of a hemangioepithelioma. Roentgen therapy was begun, and in six weeks the swelling had decreased, and the symptoms were relieved when I examined her just before my enlistment in the Army.

Photomicrographs of sections from the lesions in cases 3 and 4 are characteristic of hemangioma (figs. 1 and 2). Many of the blood vessels are thin walled

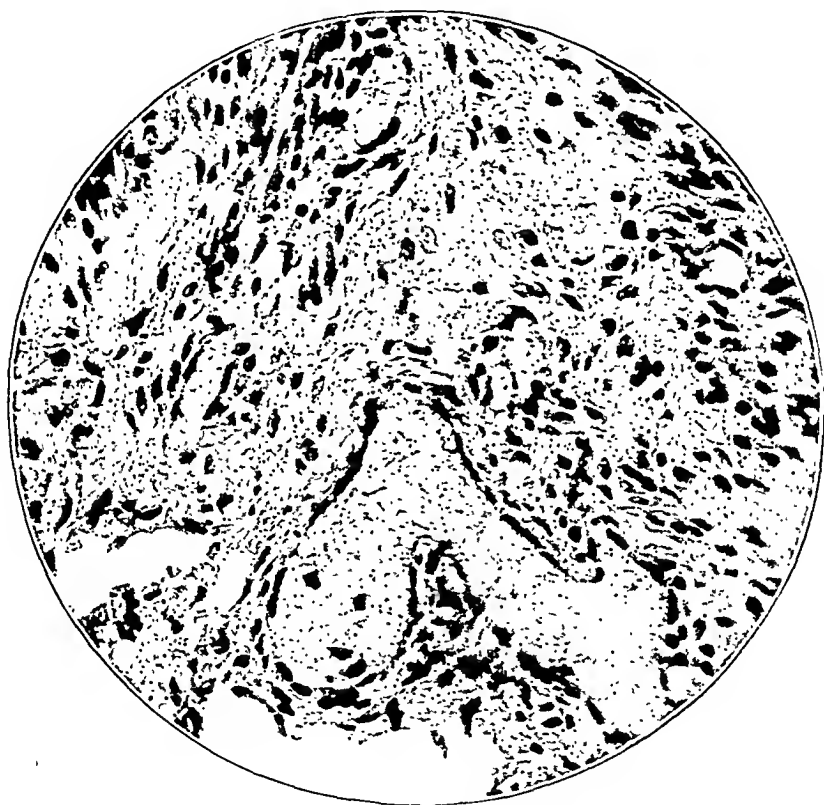


Fig. 2 (case 4).—High power photomicrograph showing a section from a hemangioma of the knee joint.

and are sharply defined. The walls of other blood vessels are continuous with broad plaques of endothelial cells, which are of uniform structure. Throughout these sections extensive and dense plasma cell infiltration and some fibrosis are present.

The historical background and the pertinent literature were thoroughly reviewed in a previously published paper.<sup>1</sup> The admitted ease of error in diagnosis was also discussed. However, hemangioma of the joints is more common, I believe, than is generally appreciated. A number of factors make it possible to suspect this tumor if not always to diagnose it before exploration. A history of hemangioma in other members of the family, the finding of hemangioma in other parts of the

body, a history of intermittent swelling over a long period of time, a decrease in the swelling on elevation of the extremity or the absence of any other positive findings in an apparently healthy patient should suggest a diagnosis of hemangioma. Aspiration as a diagnostic procedure is of little value, I believe; for unless one tears vessels with the needle or luckily happens to plunge it directly into the tumor one will aspirate normal synovial fluid.

#### CONCLUSION

I have presented 4 more cases of hemangioma of the knee joint in order to demonstrate that this tumor occurs more commonly than is often appreciated.

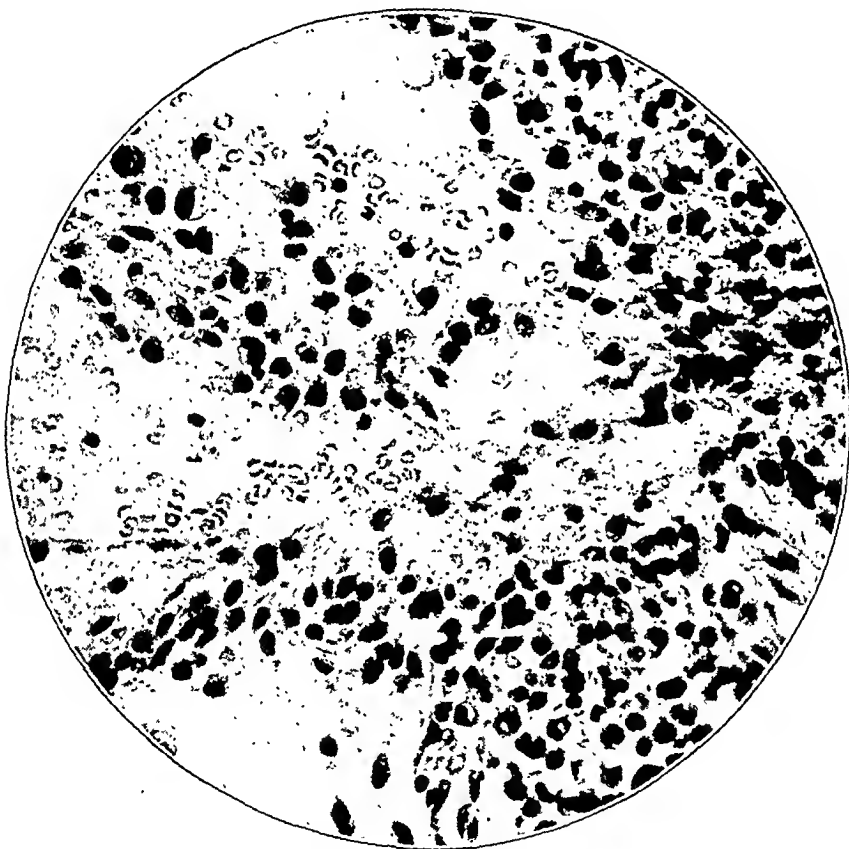


Fig. 3 (case 4).—Low power photomicrograph showing a section from a hemangioma of the knee joint.

to point out how easy it is to mistake the tumor for any one of a number of conditions that affect the knee joint and to reiterate the cardinal points in diagnosis.

The treatment is excision for pedunculated tumors and roentgen therapy for extensive lesions involving the synovial membrane and the capsule. The roentgen therapy usually requires about one week. The patient, however, should not be allowed to bear weight on the affected limb for three months after treatment is discontinued. This precaution should be taken because roentgen therapy may do damage to the growing epiphyses in a child. This risk, however, is not great.

# POST-TRAUMATIC DYSTROPHY OF THE EXTREMITIES

## A CHRONIC VASODILATOR MECHANISM

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AND

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In 1900 Sudeck described puzzling vasomotor phenomena following comparatively mild injuries occurring mainly at the wrist or ankle.<sup>1</sup> Since his original communication, a variety of terms have been employed to characterize the same syndrome, such as traumatic angiospasm, chronic traumatic edema, acute atrophy of bone, post-traumatic osteoporosis, peripheral trophoneurosis and reflex nervous dystrophy. One of us summarized the literature and added a few cases in a previous communication.<sup>2</sup> Obviously, previous authors have focused their attention on different manifestations of the same syndrome as it affects the bone, the blood vessels or the skin. While Sudeck's name is rightfully associated with this condition, he himself preferred to omit his name in subsequent communications<sup>3</sup>; atrophy is not a typical feature of the disease in its early stages.

In this report we wish to give a brief summary of our observations on this vaguely understood and frequently unrecognized syndrome. Thirty-three patients have been studied and treated; 12 of these have had repeated plethysmographic studies made and other observations relating to blood flow, vasomotor reactivity and calcium metabolism.

### REQUIREMENTS FOR EARLY DIAGNOSIS

In studying the published reports and our own series we find that severe, persistent pain of a burning character with paroxysmal aggravations presented by a patient whose injured limb is properly immobilized, noninfected and seemingly on the way toward a normal course of repair should make one suspicious of an early beginning reflex dystrophy. In this early stage the extremity is warm, the subcutaneous tissue and especially the periarticular spaces are edematous and the muscles are hypertonic in their effort to splint the painful joint. The cutaneous temperature is definitely elevated compared with that of the non-affected extremity, and the oscillations are higher. At this stage the pain is closely limited to the site of injury and its spreading character is not evident; nor is there any osteoporosis, which does not seem to occur unless hyperemia has been present continuously for from four to eight weeks.

The syndrome may stop at this point or progress to a second stage. Here the periarticular edema has spread for a considerable distance; the part is not as warm and flushed and may become hard, cyanotic and cold to touch. Because of

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1. Sudeck, P.: Ueber die acute entzündliche Knochenatrophie, *Arch. f. klin. Chir.* **62**: 147, 1900.

2. de Takáts, G.: Reflex Dystrophy of the Extremities, *Arch. Surg.* **34**:939 (May) 1937.

3. Sudeck, P.: Die trophische Extremitätenstörung durch periphere (infektiöse und traumatische) Reize, *Deutsche Ztschr. f. Chir.* **234**:596, 1931: Die kollateralen Entzündungsreaktionen an den Gliedmassen (sog. akute Knochenatrophie), *Arch. f. klin. Chir.* **191**:110, 1938.

the splinting action of the muscles and because of the synovial edema, the joints become stiff rather early, and this is one of the important residual disabilities with which one has to deal. Rheumatoid arthritis with its vascular phenomena is quite analogous to this condition. At this stage the pain is that of a spreading neuralgia.

Finally the skin becomes atrophic, the fingers or other joints are stiff, the muscles are atrophic and evidence of osteoporosis appears in the roentgenograms. There is a spotty decalcification of the small bones of the hand and foot and in the metaphyses of long bones, where vascularity is the greatest. There can be no doubt that the cause of this decalcification is hyperemia.<sup>4</sup> The mottled, spotty osseous atrophy later becomes diffuse, at which time it is indistinguishable from osteoporosis of other origin, such as that due to inactivity, senility, undernutrition or biliary fistula. We doubt that the diagnosis of Sudeck's atrophy can ever be made on the basis of roentgenograms alone. The syndrome may be present in the absence of osteoporosis, or it may be subsiding when the bony changes are at their height. The pain does not follow the course of osteoporosis, because after sympathectomy the pain may rapidly subside but the osteoporosis persists for many months. The greatest value of roentgenograms lies in serial examinations. When coarse trabeculation occurs with evidence of recalcification the peak of disability has passed. Complete restitution of osseous structure has not been seen in our roentgenograms.

#### DIFFERENTIAL DIAGNOSIS

The syndrome of Sudeck's atrophy may be so vague at first and clouded by such additional complications later that its differentiation from other conditions is not always easy. Elsewhere<sup>5</sup> we have discussed the point that reflex dystrophy is often associated with syndromes from which some authors try to separate it. Thus we are convinced that in this syndrome the early spotty osseous atrophy caused by increased blood flow to the bone is complicated later by a superimposed atrophy of disuse. Atrophy of bone seen around tuberculous or rheumatic joints must be recognized, but it may well be, as we shall point out, that this atrophy is caused by the same vasodilator mechanism which operates in the traumatic cases. Aseptic necrosis of bone causes rarefaction, but the roentgenograms do not show the ground glass appearance of Sudeck's atrophy. Senile osteoporosis is most evident in the vertebrae but may involve other parts of the skeletal system. In 3 of our cases the presence of senile osteoporosis of the spine seemed to aggravate local post-traumatic osteoporosis and make it less responsive to treatment. Other forms of osteoporosis due to hyperparathyroidism, hyperthyroidism, pituitary basophilism and adrenocortical syndromes, metastatic malignant lesions, multiple myeloma and osteomalacia have been discussed and differentiated from senile osteoporosis by Black, Ghormley and Camp.<sup>6</sup> They can hardly be confused with Sudeck's atrophy.

Finally, traumatic neurosis, compensation neurosis and malingering may have to be considered. It is here that the definite vascular changes to be described are of value. But it must be pointed out that the anxiety state of the patient may have a bearing on his autonomic reflexes and that from the standpoint of therapy all disturbing cortical and subcortical influences should be eliminated by early

4. Pommer, G.: Ueber Osteoporose, ihren Ursprung und ihre differentialdiagnostische Bedeutung, *Arch. f. klin. Chir.* **136**:1, 1925.

5. Miller, D. S., and de Takáts, G.: Post-Traumatic Dystrophy of the Extremities, *Surg., Gynec. & Obst.* **75**:558, 1942.

6. Black, J. R.; Ghormley, R. K., and Camp, J. D.: Senile Osteoporosis of the Spinal Column, *J. A. M. A.* **117**:2144 (Dec. 20) 1941.

settlements, reassurance and relief from anxiety. Again it is our feeling that instead of trying to differentiate Sudeck's atrophy from a "state of mind" the participation of this element should be ascertained, since it probably plays a role in the symptoms of injury.

The hard, traumatic edema produced artificially by a constricting band may be recognized by obtaining an infra-red picture of the suspected site of constriction, since it shows subcapillary extravasations in the form of a band.

#### STUDIES ON BLOOD FLOW IN REFLEX DYSTROPHY

One of us (D. S. M.) slightly modified the excellent water plethysmograph described by Abrahamson,<sup>7</sup> and all readings were carried out with this apparatus. The apparatus can be used for arm, hand or foot (fig. 1) and has been described in detail elsewhere.<sup>5</sup> The patients came to the laboratory early in the morning without breakfast. They were placed comfortably on a bed and rested for thirty

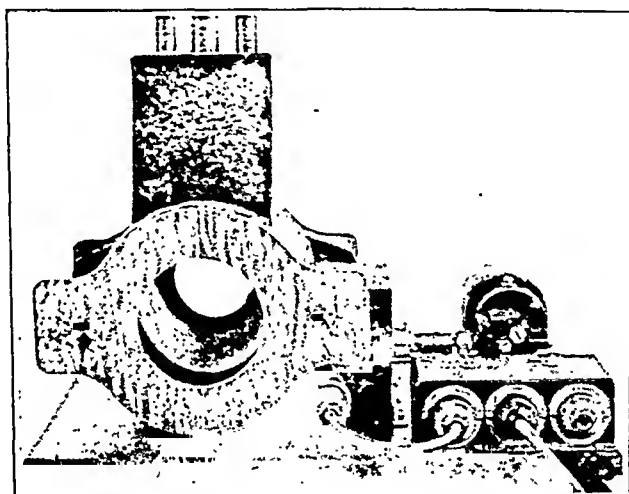


Fig. 1.—Final design of plethysmograph, the result of several modifications. The apparatus may be used for hand or foot; the temperature of the water bath is thermostatically controlled.

TABLE 1.—*Studies of Blood Flow in Post-Traumatic Reflex Dystrophy*

Case	Number of Studies	Blood Flow in Cc. per 100 Cc. of Limb Volume		Limb Volume in Cc.		Percentual Increase of Blood Flow in Affected Limb
		Affected Limb	Normal Limb	Affected Limb	Normal Limb	
1. R. H.	13	5.55	4.84	444	432	+20
2. S. O.	10	4	2.84	1,013	924	+32
3. F. O.	6	3.41	2.55	975	930	+33
4. K. W.	6	1.9	1.43	860	806	+35
5. M. B.	12	1.58	1.50	828	768	+5
6. B. S.	13	6.07	5.11	240	270	-18
7. C. B.	4	1	1.23	887	896	-23
8. R. D.	8	3.7	1.8	916	849	+48.6
9. E. L.	9	7.4	5.92	258	282	+25
10. B. M.	10	5.86	4.60	463	463	+29
11. M. Y.	11	4.49	2.80	878	826	+60
12. G. D.	12	5.12	4	935	881	+27
Total.....	114	45.26	38.42	8,707	8,427	+30.5

7. Abrahamson, D. I.; Zazecla, H., and Marrus, J.: Plethysmographic Studies of Peripheral Blood Flow in Man: I. Criteria for Obtaining Accurate Plethysmographic Data. *Am. Heart J.* 17:194, 1939.



minutes covered with a light woolen blanket. The temperature of the water bath in which the extremity was placed was 32 C. (89.6 F.) except in some instances, in which cool or hot environmental effects were studied. The results were calculated in cubic centimeters of blood per hundred cubic centimeters of limb volume. From 6 to 20 trials were made on each extremity and the average taken from them.

A total of 114 determinations were made on the injured extremities and the same number on the normal extremities of 12 patients. Table 1 shows a summary of our findings. In 11 of the 12 patients the affected limb showed an increase in blood flow, varying from 60 per cent to 5 per cent. The volume of the affected limb was also usually larger, although the increase in volume did not parallel the increase in blood flow. The patient in case 7 showed a very small basal blood flow with a low basal metabolic rate and showed an even smaller blood flow in the affected limb. As a subsequent sympathectomy revealed, there was

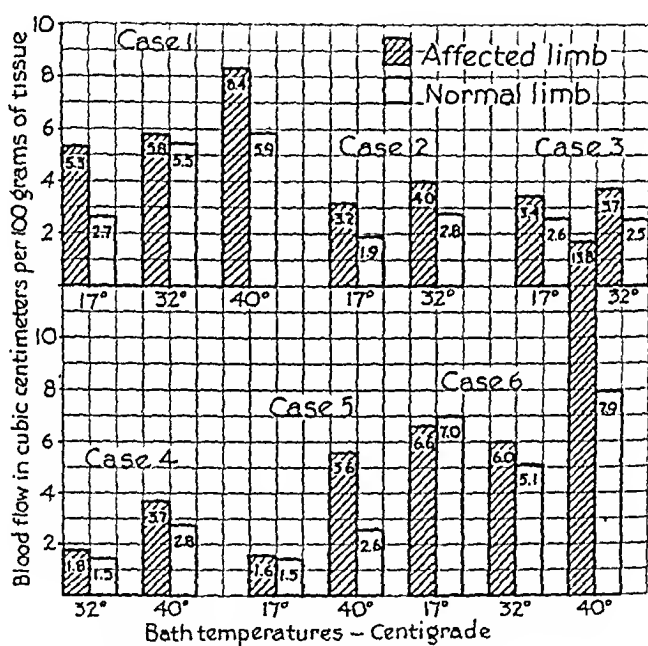


Fig. 2.—The effect of temperature on blood flow in Sudeck's atrophy.

pronounced vasoconstriction in both feet, especially in the affected extremity. In case 5, in which there was only a 5 per cent increase in flow, the disease was in a late stage of atrophy and all readings were low.

The average increase in blood flow in the 12 cases was slightly above 30 per cent in the affected extremity. This remarkable increase persisting over many months and years is the most characteristic feature of the syndrome. Its possible mechanism will be discussed in subsequent paragraphs. Of interest was the behavior of such extremities when they were subjected to changes in environmental temperature. While the room temperature was kept at 28 C. (82.4 F.), the temperature of the water bath varied from 15 C. (59 F.) to 40 C. (104 F.). Figure 2 shows that at lower temperatures the difference between the two sides was not as great as at higher temperatures. The affected extremity did not respond with vasoconstriction in a cooler bath as readily as did the normal limb. One would expect such reactions in the presence of a chronic vasodilatation. Occasionally, however, there is a masked vasoconstriction in such limbs, which may account for some paradoxical responses.

## BLOOD FLOW AFTER SYMPATHECTOMY

A total of 23 determinations of blood flow prior to and 18 following sympathectomy were made on 4 patients. In spite of the already increased blood flow on the affected side, there was a further increase following operation in 3 of 4 cases. The interpretation of these findings, together with observed clinical relief, will be given in the discussion.

## STUDIES ON CALCIUM METABOLISM

Determinations of blood calcium, phosphorus and phosphatase were made for 12 patients affected with reflex dystrophy. In 4 cases the determinations were repeated several weeks apart. While the values for calcium and phosphorus were normal, the phosphatase was slightly but definitely elevated in most instances

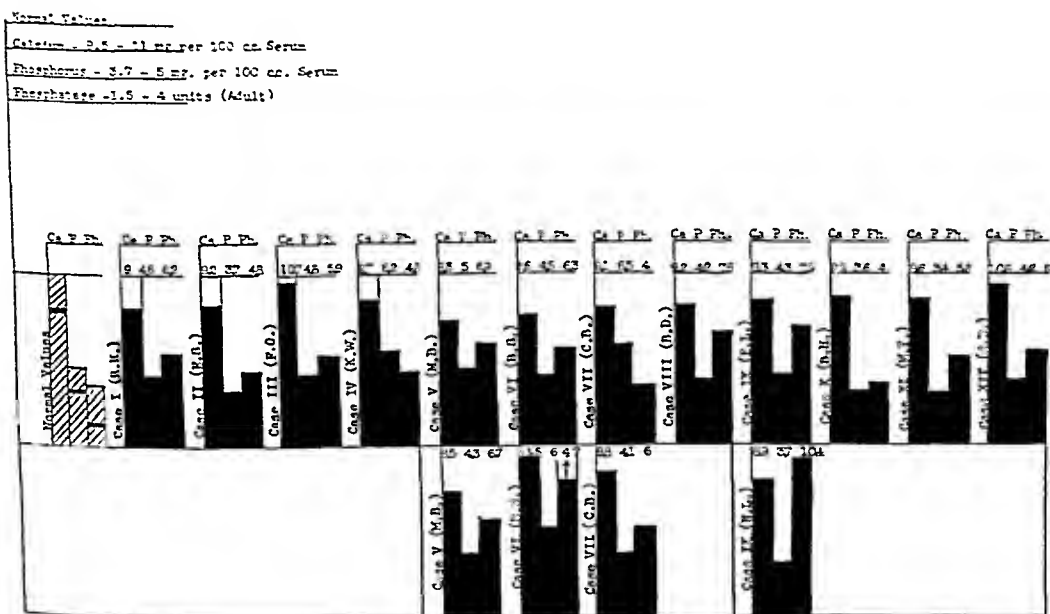


Fig. 3.—Studies of calcium, phosphorus and phosphatase in Sudeck's atrophy.

(fig. 3). The upper level of normal expressed in Bodansky units is 4. This figure was obtained in case 10 (B. H.), in which a spotty atrophy of the carpal bones developed after a blunt injury of the dorsum of the hand. Obviously only a small area of bony structure was involved. The highest reading, on the other hand, of 10.4 units, was obtained in case 9, in which the patient had a diffuse osteoporosis of the entire upper extremity following a fracture of the shoulder. This woman was 58 years old, and her traumatic osteoporosis may well have merged with a senile osteoporosis.

We have insufficient data on other forms of atrophy of bone, but it is possible that the phosphatase level may give an indication of the extent of osseous atrophy and especially of the presence of reconstructive activity.

## THE COURSE OF THE DISEASE

There are mild types of reflex dystrophy which subside spontaneously in a few weeks or rapidly respond to local or paravertebral infiltrations of procaine hydrochloride. There are types of moderate severity causing continuous pain, increasing contractures of tendons and joints and extreme decalcification of bone.

The patients are completely disabled. The course is self limited, however, and there may be spontaneous healing within a year, residual stiffness, deformity and contractures being left in spite of an insignificant original injury. There is, finally, a severe form which causes a spreading neuralgia, a spreading osteoporosis and a gradual mental fixation on the intractable lesion. The patients may request amputation or threaten or commit suicide. A functional and economic rehabilitation is hardly ever obtained. The patients may require permanent institutional care (figs. 4 and 5).

The severity of the original injury does not determine the course of the disease. Severe trauma causing fracture of long bones and total transection of nerves and blood vessels does not seem to be followed by this syndrome. Sprains, contusions, mild frostbites or burns, partial injuries to nerves and venous thromboses are in the history of patients with Sudeck's atrophy (table 2). One has the impression after studying these patients that their autonomic nervous system is

TABLE 2.—*Sudeck's Atrophy: Character of Trauma and Duration of Symptoms Prior to Treatment*

Initial Trauma	Number of Cases	Duration of Symptoms in Months
Sprined ankle.....	8	8, 2, 4, 4, 3, 12, 42, 5
Sprained ankle and fractured fibula.....	2	5, 24
Dislocated ankle.....	1	7
Infection at inner ankle.....	1	5
Sprained wrist.....	2	1, 8
Wringer injury to wrist.....	2	7, 36
Colles' fracture.....	1	12
Crushed finger.....	4	12, 6, 6, 45
Blunt injury to dorsum of hand.....	2	1, 1
Fracture of navicular bone.....	1	15
Blunt injury to dorsum of foot.....	1	5
Injury to shoulder.....	2	9, 78
Periphrlebitis.....	4	36, 36, 8, 20
Blunt injury to lower leg.....	1	14
Scar following incision of toe.....	1	6
Total number of cases.....	33	

unstable. One cannot help referring to animal experiments which indicate that when cortical release is produced by decortication an autonomic reflex, such as gastric contraction after stretching, is exaggerated.<sup>8</sup> There are also clinical observations to show that a hemiplegic extremity shows overactivity of the sympathetic nervous system.<sup>9</sup> It would seem, then, that certain emotional states, such as anxiety and fear, as well as uncontrolled pain, are capable of facilitating vascular reflexes which normally subside in a few days.

#### THE NATURE OF THE REFLEX

In figure 6 we have summarized our concept of vascular reflexes arising from traumatic stimuli in the extremities. Trauma in the broad sense of the word may consist of a mechanical, chemical or thermal injury or a vascular occlusion. Somatic sensory fibers carry impulses centrally from such an area. In *A* the nerve impulse never reaches the cord but produces an efferent vasodilatation, an axon reflex. In *B* vasodilatation has been activated through a spinal cord reflex. This pathway is

8. Hesser, F. H.; Langworthy, O. R., and Kolb, L. C.: Experimental Study of Gastric Activity Released from Cortical Control, *J. Neurophysiol.* 4:274, 1941.

9. Pilcher, C.; Wyatt, T. E., and Carney, H. M.: Infarction of the Brain with Unilateral Circulatory Changes, *Arch. Neurol. & Psychiat.* 45:321 (Feb.) 1941.



Fig. 4.—Minnie B., a 46 year old woman, twisted her ankle. She immediately complained of severe, continuous pain. At an emergency station a fracture of the fibula was diagnosed. A posterior molded splint was applied. Two weeks later another cast was applied. After the second cast had been worn for five weeks, adhesive strapping was used. She still had continuous pain and could not bear weight on the foot. Because of the disproportion between the pain and the solidly healed fracture, malingering was suspected. A general anesthetic was given, and during the first stage moderate pressure, which elicited a painful response, was applied to the injured ankle.. At the time she was first seen by one of us (D. S. M.) the foot was in a pronounced equinus position, the skin was glossy and cyanotic and the ankle was swollen. There was an increased growth of hair on this area, and the nails were ribbed. The patient refused all therapy and at the time of writing remains incapacitated.



Fig. 5.—Roentgenograms of Minnie B. taken two years after she suffered a sprained ankle with a fracture of the fibula. The bones of the left foot show a diffuse osteoporosis and a "ground glass" appearance. Roentgenograms of both hips and of the spine showed a moderate osteoporosis. The osteoporosis was first visible two months after the injury and was first a spotty type of atrophy, which gradually became diffuse.

postulated by Toennies,<sup>10</sup> but its existence is denied by Dole and Morison.<sup>11</sup> In C the efferent sympathetic vasoconstrictors have been activated, but vasodilatation is also possible through the sympathetic outflow.

It seems to us that, as was shown by Albert<sup>12</sup> in 1924 for the dog, all trauma results in vasomotor reactions which, unlike the much emphasized reflex vasoconstrictions, are predominantly vasodilator. Applied to the present problem of Sudeck's atrophy, the vasodilator reflexes first predominate, but may give way later to vasoconstriction.

In figure 7 we illustrate the axon reflex more in detail. Its persistence and gradual spread is consistent with the clinical picture of Sudeck's atrophy. In this diagram the stimulus *b* is shown to spread centripetally to the next division, from which it travels centrifugally, but it also travels in a centrifugal direction from the point of stimulation. This type of spread would explain the observation of Tinel,<sup>13</sup> confirmed by Sir Thomas Lewis,<sup>14</sup> that blocking or sectioning of a peripheral nerve distal to the source of irritation may bring relief.

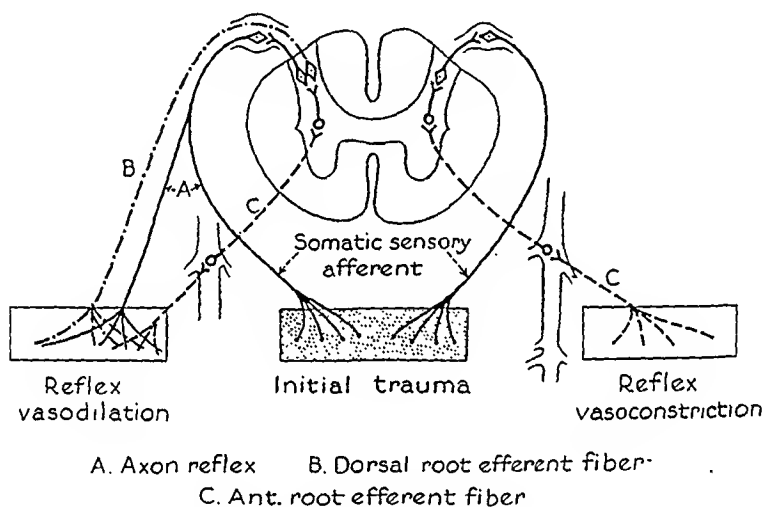


Fig. 6.—Vasomotor reflexes of the extremities.

#### THE VALUE OF SUCH A WORKING HYPOTHESIS

The diagrams shown have a definite value in outlining treatment. If the syndrome is recognized within the first few weeks, when osteoporosis is not even present, the repeated block of the local area, together with satisfactory immobilization, may abort the disease. It is a curious fact that men like Böhler,<sup>15</sup> who strictly immobilize most injuries but encourage early weight bearing and active motion, either have not seen the syndrome under discussion or have not deemed it worthy of mention. The early control of continuous nerve stimulation seems.

10. Toennies, J. F.: Reflex Discharge from the Spinal Cord over Dorsal Roots, *J. Neurophysiol.* 1:378, 1938.

11. Dole, V. P., and Morison, R. S.: A Note on the Question of Reflex Activation of Dorsal Root Dilators, *Am. J. Physiol.* 130:304, 1940.

12. Albert, F.: Étude expérimentale des troubles vaso-moteurs réflexes d'origine traumatique, *Arch. internat. de physiol.* 22:391, 1924.

13. Tinel, J.: *Le système nerveux végétatif*, Paris, Masson & Cie, 1937.

14. Lewis, T.: Experiments Relating to Cutaneous Hyperalgesia and the Spread Through Somatic Nerves, *Clin. Sc.* 2:373, 1936.

15. Böhler, L.: Treatment of Fractures, translated by M. E. Steinberg, Vienna, Wilhelm Maudrich, 1929.

then, of importance. It is more difficult to explain the value of repeated sympathetic blocks, although clinically there can be no doubt about their efficacy in early stages. The same difficulty is encountered in explaining the benefit of sympathectomy for patients with the more advanced conditions. There are three possible explanations which need to be examined.

First, it is possible that the painful stimuli which give rise to vasodilatation travel centripetally in the sympathetic fibers. It is true that a sympathetic block promptly abolishes the causalgia or burning pain of this syndrome, but it does not abolish the vasodilatation. The pain, then, is not due to vasodilatation, at least not to the kind that results from blocking the vasoconstrictors. It would seem that afferent sympathetic fibers, whose existence in the periphery is denied by the great majority of investigators, are not involved.

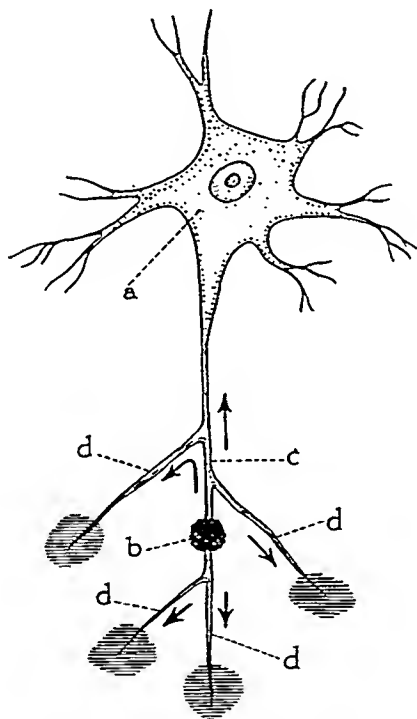


Fig. 7.—The axon reflex shown in figure 6 is reemphasized in this diagram. The stimulation of the nerves results in the production of pain-producing substances. Unless somatic sensory nerves are capable of antidromic conduction, such phenomena postulate the existence of posterior root efferent fibers, a theory which is supported by the persuasive evidence of Toennies.<sup>10</sup>

The second possibility is that the vasodilatation in Sudeck's atrophy is transmitted by efferent vasodilators in the sympathetic nervous system. There is no doubt about their existence in man.<sup>16</sup> However, if this mechanism were operative one would expect a decrease of blood flow after sympathectomy, whereas the increase in blood flow persists in spite of the relief from pain.

The third possibility is that the vasodilator efferent fibers of the posterior root system, which are stimulated directly or reflexly by the injury, secrete a pain substance which is diffusible and which would explain the peculiar type of hyper-

16. Lewis, T., and Pickering, G. W.: Vasodilation in the Limbs in Response to Warming the Body, with Evidence of Sympathetic Vasodilator Nerves in Man, *Heart* 16:33, 1931.

esthesia encountered in Sudeck's atrophy. These fibers correspond to the "nocifensor system" of Sir Thomas Lewis.<sup>14</sup> Sympathectomy, then, would not interfere with any nervous pathway but might "wash out" or eliminate the pain substance.<sup>17</sup> Similarly herpes zoster, which is due to an irritation of the posterior root system, can be rendered painless and made to heal after paravertebral block.<sup>18</sup>

We have no conclusive evidence for the last explanation but have used it as a working hypothesis. It may be that sympathectomy, as Hyndman and Wolkin<sup>19</sup> recently stated, results in capillary constriction and thus eliminates some of the vasodilatation, but this would hardly explain the relief of pain that this operation affords.

#### TREATMENT

For the disease in the early, mild stage, sufficient immobilization and repeated infiltrations of procaine hydrochloride into the injured area seem almost specific. When the neuralgia has spread beyond the site of injury, the glove or stocking type of hyperalgesia may be successfully treated by paravertebral injections of procaine hydrochloride. As Homans<sup>20</sup> pointed out, these injections may give relief for a longer and longer period until the pain is entirely abolished. When sympa-

TABLE 3.—Results of Treatment in Sudeck's Atrophy

Type of Treatment	Number of Cases	Recovery *		
		Complete	Partial	None
Cast, splint, physical therapy.....	5	1	3	4
Repeated procaine block.....	1	..	1	..
Repeated sympathetic block.....	5	4	1	..
Periarterial sympathectomy.....	3	2	1	..
Perivenous stripping.....	2	2	..	..
Sympathetic ganglionectomy.....	3	5	3	..
No treatment.....	6	..	2	4
Total.....	33	14	11	8

\* Complete recovery, restoration of function; partial recovery, cessation of pain with limitation of function; no recovery, stationary or deteriorating physical or mental status.

thetic block abolishes the symptoms but they recur with undiminished intensity after a few hours or days, sympathetic ganglionectomy is not to be postponed. There is, finally, a group of cases of a severe, intractable form of the disease associated with compensation neurosis, drug addiction and mental imbalance which may be caused in part by continuous suffering, for which treatment is of no avail.

Table 3 summarizes the various forms of treatment employed. Since some of the patients were seen late, after contractures, ankylosis and severe osteoporosis had developed, the efficacy of treatment cannot be judged without considering the stage of the disease at the same time. Generally speaking, conservative treatment may lead to a slow, spontaneous regression of the disease with cessation of pain and recalcification of bone; however, the changes in the joints and the shortening of the tendons allow only a partial recovery. Repeated block with procaine hydrochloride was employed in only 1 case, in which today we should prefer sympathetic block. Periarterial sympathectomy resulted in complete recovery in 2 cases and partial

17. Gask, G. E., and Ross, J. P.: *The Surgery of the Sympathetic Nervous System*, ed. 2, Baltimore, William Wood & Company, 1937.

18. de Takáts, G., and Miller, D.: Unpublished data.

19. Hyndman, O. R., and Wolkin, J.: *The Autonomic Mechanism of Heat Conservation and Desiccation: I. Effects of Heating the Body*, *Am. Heart J.* **22**:289, 1941.

20. Homans, J.: *Minor Causalgia Following Injuries and Wounds*, *Ann. Surg.* **113**:932, 1941.

recovery in 1 case, but with increasing experience we would prefer repeated sympathetic blocks for these patients. Perivenous stripping in 2 patients suffering from reflex dystrophies following venous occlusion has been successful. Sympathetic ganglionectomy gave excellent results in 5 and fair results in 3 patients. In the latter group, 1 operation was incomplete; in the other 2 cases changes in the joints and tendons were so far advanced that orthopedic correction became necessary.

Of the 8 patients who obtained no relief, 4 were treated conservatively and 4 refused any type of treatment. Two of this group are in closed institutions, 2 could not be traced and 4 have litigations pending.

#### CONCLUSIONS AND SUMMARY

It is our impression, on the basis of clinical observations, studies on blood flow and results of treatment, that the syndrome of Sudeck's atrophy is the result of a chronic stimulation of somatic and possibly of efferent vasodilator fibers; the reflex may soon subside, or it may become chronic and progressively increasing in its effects. Pain, localized and spreading, vasodilatation and osteoporosis characterize the fully developed syndrome, but osteoporosis is a comparatively late manifestation. In fact, reflex dystrophy is most amenable to treatment in the early weeks and months; it becomes more intractable and requires more and more radical intervention if early treatment is not instituted. The trauma which it follows is usually a blunt injury near a joint or a nerve trunk, such as the interosseous, the saphenous or the posterior tibial nerve. The part is often inadequately immobilized. The emotional status of the patient may well exaggerate these phenomena, as cortical release often does in case of autonomic reflexes.

The treatment must fit the duration and severity of the syndrome and consists of repeated injections of procaine hydrochloride into the injured area, paravertebral sympathetic block, periarterial sympathectomy and sympathetic ganglionectomy. Orthopedic correction may be needed in the cases of advanced atrophy after the pain has subsided.



# SOLITARY BENIGN ENCHONDROMA OF BONE

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By solitary benign enchondroma of bone we mean the benign cartilaginous growth which begins its development in the interior of an affected bone and involves only a single bone in any 1 subject. Our records include 28 instances<sup>1</sup> of this type of lesion, and the discussion which follows is based largely on these. To judge from our experience, the lesion appears mainly in phalanges (particularly those of the hand), in metacarpal bones and in the humerus and femur, though other bones of the limbs are occasionally the site. Although our own cases do not include any in which the lesion was in a bone other than one of a limb, it should be noted that instances of such localization have also been reported.

A benign enchondroma may be present in the interior of a bone without causing any obvious distention. However, it is not unusual to find, especially if the lesion is in a short tubular bone (phalanx or metacarpal or metatarsal bone), that some part of the affected area is distended in consequence of thinning and bulging of the overlying cortex. Still, the mere fact that the central cartilaginous growth has strongly bulged out the overlying cortex for some distance should not lead, as it often does, to clinical misinterpretation of such an enchondroma (central chondroma) as an osteochondroma (osteocartilaginous exostosis).

For a long time it has been known that a benign enchondroma may undergo malignant transformation into a chondrosarcoma. This is by no means a rare occurrence in connection with an enchondroma in a long tubular bone. Indeed, in a number of cases of central chondrosarcoma of such a bone which we have studied<sup>1a</sup> we have been able to trace the evolution out of an originally benign central chondromatous lesion. The transition is usually slow, and indeed years may elapse before one is finally faced with an obvious chondrosarcoma.

Most of the contemporary papers dealing with solitary benign enchondroma present accounts of single cases or at most 2 or 3 and stress the clinical details and often particularly the relevant surgical procedures rather than the pathologic changes. From some of the reports it is impossible to tell whether a particular case actually represents an enchondroma (central chondroma) or an osteochondroma (osteocartilaginous exostosis). Often an article does not even contain a statement as to whether a given enchondroma (or, more vaguely, chondroma) discussed was a solitary lesion or was associated with similar lesions in other skeletal parts. That is, cases of solitary enchondroma are sometimes not distinguished from cases of dyschondroplasia (skeletal enchondromatosis; Ollier's disease). Finally, one is sometimes unable to decide on the basis of the information reported in a paper whether a given lesion is still a benign enchondroma or, as one suspects from the general picture, has become a chondrosarcoma.

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From the Laboratory Division, Hospital for Joint Diseases.

1. Since the time of writing, we have studied 2 additional cases. In 1 case, the lesion was in the terminal phalanx of the third finger of a woman of 37. In the other, it was in the fifth metacarpal bone of a girl of 19.

1a. Lichtenstein, L., and Jaffe, H. L.: Chondrosarcoma of Bone, *Am. J. Path.*, to be published.

It is our intention in this paper (1) to sketch the clinical and roentgenographic findings in cases of solitary benign enchondroma; (2) to consider the pathologic (and especially the cytologic) structure of the lesion; (3) to indicate the cytologic changes which appear if the lesion is undergoing transformation into a chondrosarcoma, and (4) to point out the bearing of these various considerations on the management of pertinent cases.

#### CLINICAL ASPECTS

*Sex and Age Incidence.*—Of the patients in our series of 28 cases, 12 were males and 16 females; that is, there seems to be no significant sex difference in incidence. In respect to age of the patients at the time of admission to the hospital for treatment, only 1 was under 10 and only 1 over 50 years of age while 16 were between 11 and 30 and 10 between 30 and 50. As to age at onset of the complaints, it appears that the history was sometimes one of only a few weeks or months but sometimes one of many years, irrespective of the age on admission. It should be pointed out, however, that in connection with involvement of a humerus or femur (as compared with the involvement of other bones) the interval between the onset of clinical manifestations and the time of admission was consistently short. Except in 1 instance, in which it was one and one-half years, it uniformly amounted to only some weeks or months. Possibly this is explicable through the greater disability involved and the consequently greater attention given when clinical manifestations start to appear in relation to long bones.

*Localization.*—Apparently, as already noted, solitary benign enchondroma has a predilection for limb bones. As to the site of the lesion in our 28 cases, this was a finger phalanx in 13, a metacarpal bone in 5, a humerus in 5, a femur in 3, a toe phalanx in 1 and a metatarsal bone in 1. Indeed, the lesion is found in bones of the hand in particular, and our findings in this respect are in harmony with those of Mason.<sup>2</sup> Evidently, to judge from our material, which seems fairly representative, localization of the lesion in a toe phalanx or a metatarsal bone is not as common as certain blanket statements in the literature would lead one to believe. If these blanket statements are checked against actual case reports, it appears that relatively few of these reports relate to lesions in toe phalanges or metatarsal bones. As to localization in long tubular bones, however, our findings are in accord with those reported in the literature in suggesting that among these the humerus and femur are the most likely to be affected. In regard to involvement of ribs, pelvic bones, vertebrae or skull bones, which is by no means common, it is often difficult to be certain of the point of origin and the real nature of the lesion, as is pointed out by Menne and Frank,<sup>3</sup> for instance, in respect to certain chondromas in bones of the skull.

Benign enchondromas of short or long tubular bones begin their development in the metaphysis as a rule, although by no means always (see footnote 4). A central chondroma beginning within a metaphysis may eventually involve a large portion of the shaft and even extend into the corresponding epiphysal end of the affected bone. It by no means necessarily grows into the adjacent epiphysis, however, and apparently does not do so in any case until the epiphysis has fused with the shaft; that is, it does not tend to violate the epiphysal cartilage plate.

According to the prevailing view, benign enchondromas of bone arise from misplaced cartilage rests. In relation to lesions developing in the metaphysis of tubular bones, the source of these rests is generally stated to be cartilage snared

2. Mason, M. L.: Tumors of the Hand, Surg., Gynec. & Obst. **64**:129 (Feb.) 1937.

3. Menne, F. R., and Frank, W. W.: So-Called Primary Chondroma of the Ethmoid. Arch. Otolaryng. **26**:170 (Aug.) 1937.

off from an epiphysial cartilage plate. The principal basis for this conception has been that at autopsy in cases of healing rickets foci of cartilage apparently derived from the cartilage plates have been found in the metaphyses of tubular bones.

Possibly even in persons who have not had rickets, cartilage apparently derived from the cartilage plates may be found persisting in the metaphyses, even into old age. Indeed, Scherer,<sup>3a</sup> from Schmorl's laboratory, stated that lentil-sized to cherry-pit-sized cartilage rests were found in the right femur in 20 of 1,125 cases (1.7 per cent) in which this bone was routinely removed and examined. The subjects were all over 25 years of age. The rests were found in the metaphyses of the femur, at most a few centimeters from an epiphysial cartilage plate, with a heavy predilection for the upper metaphysis. The rests usually showed considerable evidence of regressive change, the cartilage having undergone a good deal of calcification and cystification in some cases and even heavy ossification in others. Undoubtedly, many cartilage rests, after undergoing involution, may eventually completely disappear. However, Scherer cited the case of a woman of 58 in whom, as an incidental finding at autopsy, an enchondroma measuring 8.5 cm. in length was noted in the upper metaphysis of the right femur. This lesion was believed to have evolved out of a rest such as those just mentioned which subsequently underwent a spurt of growth instead of regressing completely or at least remaining static. This case was presented by Scherer as evidence in favor of the view that solitary benign enchondroma may originate from a cartilage rest snared off from an epiphysial cartilage plate.

*Clinical History.*—A common history in the cases of phalangeal involvement was that the patient was not aware of anything wrong until a local trauma was followed by pain and swelling and a roentgenogram revealed an altered phalanx with a pathologic fracture. On the other hand, some patients gave a history of a spontaneous, not particularly painful or only intermittently painful swelling of the region of the affected phalanx, dating back perhaps several years but recently exacerbated by a local trauma. The general mildness of the clinical complaints is further attested by the fact that the condition often ran through several episodes of local trauma and disability, indicating repeated fractures through the affected phalanx. On examination, one can usually palpate at least a limited enlargement of this phalanx. The enlarged region is likely to be rather firm, and if there has been a recent fracture through the area there may be considerable local tenderness and even some heat.

The history patterns in the cases of involvement of metacarpal and metatarsal bones were essentially the same as in those of phalangeal involvement. The patients usually also presented a local swelling of the affected bone, and when there was pain (apparently from a fracture) after trauma the pain subsequently subsided though the swelling persisted.

In the cases in which long bones were affected, the clinical complaints, as already noted, were usually of rather recent date. Nevertheless, it seems probable that in these cases the lesion had been present for a long time, often for years, though latent, before the onset of manifestations. Thus, for instance, in 1 patient, a physician, the lesion was discovered by chance seventeen years before it began to cause any trouble, and then the difficulty, of two and one-half months' standing, ensued when a pyogenic infection became superimposed on the enchondroma in a femur. Another patient, a woman who showed in a femur a heavily calcified

3a. Scherer, E.: *Exostosen, Enchondrome und ihre Beziehung zum Periost*, Frankfurt. Ztschr. f. Path. 36:587a 1928.

enchondroma which must have been in existence for many years, presented herself only because of local pain of six months' duration aggravated by walking and possibly attributable to a new spurt of growth of the lesion. Still another patient, a young girl who presented an extensive lesion in a humerus, was admitted because of pain, tenderness and disability attributable to a pathologic fracture ten days previously, but she stated that a year before there had been a fracture through the same area, which had healed promptly.<sup>4</sup>

#### ROENTGENOGRAPHIC FINDINGS

*Phalanges.*—In phalanges (fig. 1 *A, B, C, D* and *E*), the lesion appears as a more or less oval rarefaction shadow. This may be situated centrally within the affected bone and may even fail to cause distention of the neighboring cortex. On the other hand, it may be situated off to one side (eccentrically) and may even cause a pronounced bulging distention and thinning of the overlying cortex. Those enchondromas which are situated eccentrically usually show a delicate radiopaque line where they abut on the uninvolved portion of the phalanx. The rarefaction shadow as a whole usually looks more or less cloudy and may present a vaguely trabeculated appearance and even densifications ranging in size from that of a pinhead to that of the head of a match. These densifications reflect foci of ossification in the cartilage and constitute telltale indications of an enchondroma. Frequently, one can note evidence of a still unhealed fracture. As also shown by these roentgenograms, as long as the epiphysis has not fused with the shaft, the former is not involved, and even after fusion the epiphysis is not necessarily invaded.

Solitary benign enchondroma is by far the most common and indeed the principal solitary lesion affecting phalanges. In fact, any lesion situated in a middle or proximal phalanx of a finger and presenting anything like the roentgenographic picture described and illustrated is almost certainly a benign enchondroma. Nevertheless, a benign enchondroma is not infrequently misdiagnosed roentgenographically as a cyst, a giant cell tumor or an osteochondroma. As already pointed out elsewhere,<sup>5</sup> solitary bone cyst of the type commonly occurring in long tubular bones rarely (if ever) occurs in phalanges, and indeed we ourselves have never seen it in the latter. As to giant cell tumor, in the strictly limited sense in which we understand this lesion,<sup>6</sup> we have never observed it in a phalanx, though we must allow for the bare possibility of its occurrence in such a bone. At any rate, in tubular bones it seems never to start its development elsewhere than in the epiphysal end of the bone, in contrast to enchondroma, which practically always starts its development in the metaphysal shaft region of such a bone. An enchondroma which has conspicuously distended part of the cortex may be misinterpreted as an osteochondroma if attention is concentrated on the bulge to the neglect of the appearance of the interior of the bone.

4. We have not included in this paper a case of solitary benign enchondroma in which the lesion began its development in an epiphysis and was confined to the latter. It seems expedient to give it at least brief mention. The lower epiphysis of a femur was the site of the lesion, and the patient was a child of 1½ years at the time of admission to the hospital. It is interesting that during the subsequent four years, before the lesion was resected and while it was enlarging until it occupied practically the entire condyle, it did not break through the plate and extend into the shaft. The lesion was originally treated by irradiation, without benefit, and indeed the growth even continued to enlarge under this treatment, although the irradiation was conducted strictly along accepted lines.

5. Jaffe, H. L., and Lichtenstein, L.: Solitary Unicameral Bone Cyst, *Arch. Surg.* 44:1004 (June) 1942.

6. Jaffe, H. L.; Lichtenstein, L., and Portis, R. B.: Giant Cell Tumor of Bone, *Arch. Path.* 30:993 (Nov.) 1940.

The only two solitary lesions which occur in phalanges (though rarely) and which may also simulate enchondroma roentgenographically are squamous epithelium-lined cyst and ossifying fibroma. Epithelium-lined phalangeal cyst<sup>7</sup> seems to occur exclusively in terminal phalanges of fingers and indeed nearly always in the terminal half of such a phalanx, a site which is rare for benign enchondroma. When occurring in digits, ossifying fibroma (osteogenic fibroma), so far as our experience is concerned, is likewise located in terminal phalanges, but of toes, not of fingers, a location again extremely rare for a solitary enchondroma.

*Metacarpal and Metatarsal Bones.*—In regard to metacarpal and metatarsal bones (fig. 1 *F, G* and *H*), the roentgenographic findings are essentially similar to those in regard to phalanges. It is to be noted, however, that in metacarpal

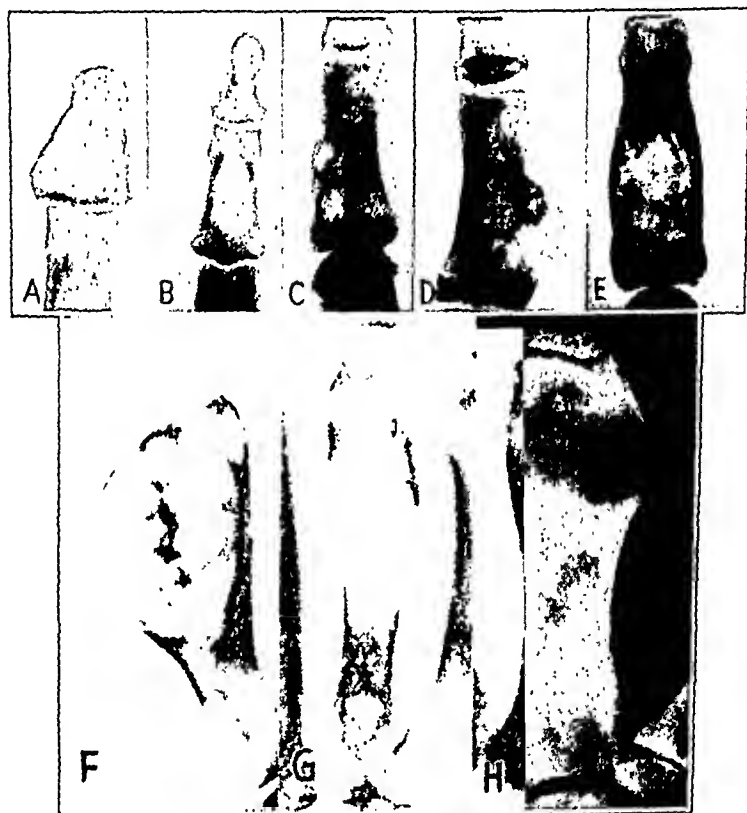


Fig. 1.—*A, B, C, D* and *E*, roentgenograms from 5 different cases, illustrating various roentgen aspects of solitary benign enchondroma in phalanges, as discussed in the text. The nature of all these lesions was verified by examination of the tissue. *F, G* and *H*, roentgenograms from 3 different cases, illustrating various aspects of solitary benign enchondroma in metacarpal bones, as discussed in the text. The nature of all these lesions was verified by examination of the tissue.

or metatarsal bones the enchondroma tends to be more or less in the distal instead of the proximal part of the shaft, though it is thus still oriented toward the epiphysis of the bone. The remarks on the differential diagnosis so far as they pertain to solitary unicameral cyst, giant cell tumor and osteochondroma apply as closely to metacarpal or metatarsal as to phalangeal enchondroma. Epithelium-lined inclusion cyst apparently does not occur in a metacarpal or metatarsal bone.

<sup>7</sup> Bissel, A. D., and Brunschwig, A.: Squamous Epithelial Bone Cysts of the Terminal Phalanx and Benign Subungual Squamous Epithelial Tumor of Finger, *J. A. M. A.* **108**:1702 (May 15) 1937.

Ossifying fibroma (osteogenic fibroma) or a solitary focus of fibrous dysplasia,<sup>8</sup> however, apparently occasionally does occur in a metacarpal or metatarsal bone. Roentgenographically, such a lesion in a metacarpal bone could simulate an enchondroma quite closely. Merely on the basis of probability, however, the likelihood is greater that one would be dealing with enchondroma, the latter being the

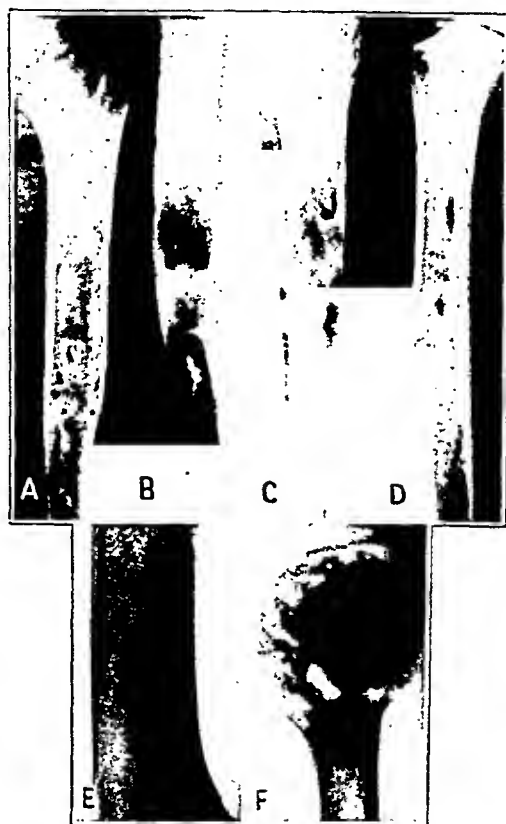


Fig. 2.—Roentgenograms illustrating various appearances presented by solitary benign enchondroma in long bones and verified by examination of the tissue. In *A*, the presence of radiopaque spots and blotches in the metaphysis and the rest of the shaft is already strong evidence in favor of the diagnosis of enchondroma. In *B*, the same is also true, and the patient (a physician) knew of the presence of this lesion for seventeen years. (Figure 4 *B* shows calcifying cartilage from one of the radiopaque areas.) In *C*, the roentgenographic picture is ambiguous. Specifically, the roentgenogram is more strongly suggestive of fibrous dysplasia than of enchondroma. In *D*, too, the diagnosis would be difficult to make on the basis of the roentgenogram alone. (Figure 3 *B* represents cartilage tissue taken from the area of rarefaction.) *E* shows the roentgenogram of a strictly central calcifying and ossifying enchondroma in the lower part of the shaft of a femur. (Figure 3 *A* represents tissue from this lesion). *F* shows a highly calcified and ossified enchondroma involving the upper end of the shaft and the head of the humerus. At the time this roentgenogram was taken, the lesion was already beginning to undergo transition into a chondrosarcoma. (Figure 5 represents tissue obtained from this lesion on two occasions ten months apart.)

8. Lichtenstein, L., and Jaffe, H. L.: Fibrous Dysplasia of Bone: A Condition Affecting One, Several, or Many Bones, the Graver Cases of Which May Present Abnormal Pigmentation of Skin, Premature Sexual Development, Hyperthyroidism, or Still Other Extraskeletal Abnormalities, *Arch. Path.* 33:777 (June) 1942.

more common lesion in the bones in question. Should the lesion present stippled foci of densification, one would have strong evidence of its actually being an enchondroma.

*Long Bones.*—In regard to long bones (fig. 2), much of what has been said about the roentgen findings in enchondroma of a phalanx or a metacarpal bone is still applicable. A considerable part of the shaft may be involved, and the lesion is likely to be more strictly central. If the cortex does bulge, it is probable that the bulge will be slight and limited to a relatively small area. The presence of spotty or blotchy calcification points rather definitely in the direction of an enchondroma. Indeed, even a few scattered pinhead-sized to match-head-sized spots of densification would point in that direction. On the other hand, when the presence of radiopaque spots is doubtful or when they are absent entirely, the diagnosis of enchondroma cannot be made with any confidence. Especially if the lesion (of course solitary) also appears somewhat expanded and trabeculated, the strongest likelihood is that it represents a solitary focus of fibrous dysplasia, and another, though weaker, possibility is that it represents a solitary unicameral bone cyst rather than an enchondroma.

#### PATHOLOGIC ASPECTS

One does not often have the opportunity of examining a solitary enchondroma intact in its setting, for ordinarily the gross material available from a lesion consists merely of fragments of cortex from the site of surgical entry and curettings from the interior of the affected area of bone. The material consisted of these in all but 2 of the 28 cases discussed here. In these 2<sup>o</sup> cases intact lesions were examined, 1 in a surgically extirpated metacarpal bone and the other in a surgically resected lower end of a femur.

The extirpated metacarpal bone showed general bulging of the contour of its shaft anteriorly, exaggerated on the distal half by two distinct hemispherical bulges, a smaller and a larger one. Sectioning of the bone in both the longitudinal and transverse axes revealed that the marrow cavity of the shaft was substantially filled by cartilage tumor tissue, which in general was bluish white and faceted. Where the contour of the bone was distended, it could be seen that tumor cartilage was bulging forward under an attenuated cortex. In the region of the two humps, the cortex had been reduced to paper thinness.

The specimen from the lower end of the femur showed when sawed sagittally an eccentrically situated tumor mass of the size of a large walnut. The tumor hugged the cortex on one side but did not distend it and was so located also that about half of its mass was situated in the lower end of the diaphysis and half extended into the epiphysial end of the bone. The tumor was so highly calcified and ossified that it appeared, on the whole, yellowish and gritty, though islands of tissue clearly recognizable as cartilage were still in evidence.

On the basis of the material from the other cases, it can be said in general that the fragments of cortical bone will be found thin and even shell-like if they come from an affected area where the cortex has been bulged out, as is commonly the case when the lesion is in a phalanx or a metacarpal or metatarsal bone. On the other hand, the cortical fragments may show but little thinning or none if they come from a lesion which has failed to bulge the cortex, a state of affairs not uncommon when a long tubular bone is affected. The medullary surface of the cortical fragments, whether they are only slightly or greatly thinned, usually shows some erosive ridging and grooving. The periosteal surface is

9. These 2 specimens are from the collection of pathologic material preserved by the late Viennese pathologist Jacob Erdheim and now housed in the laboratory of this hospital.

ordinarily found smooth and without evidence of apposition of new bone unless the cortical fragments have come from a site of recent infraction.

The tissue obtained by curettement from the interior of the lesion consists in some cases almost entirely of faceted bits of bluish white, firm or even somewhat myxomatous hyaline cartilage. However, such lesions may also yield some

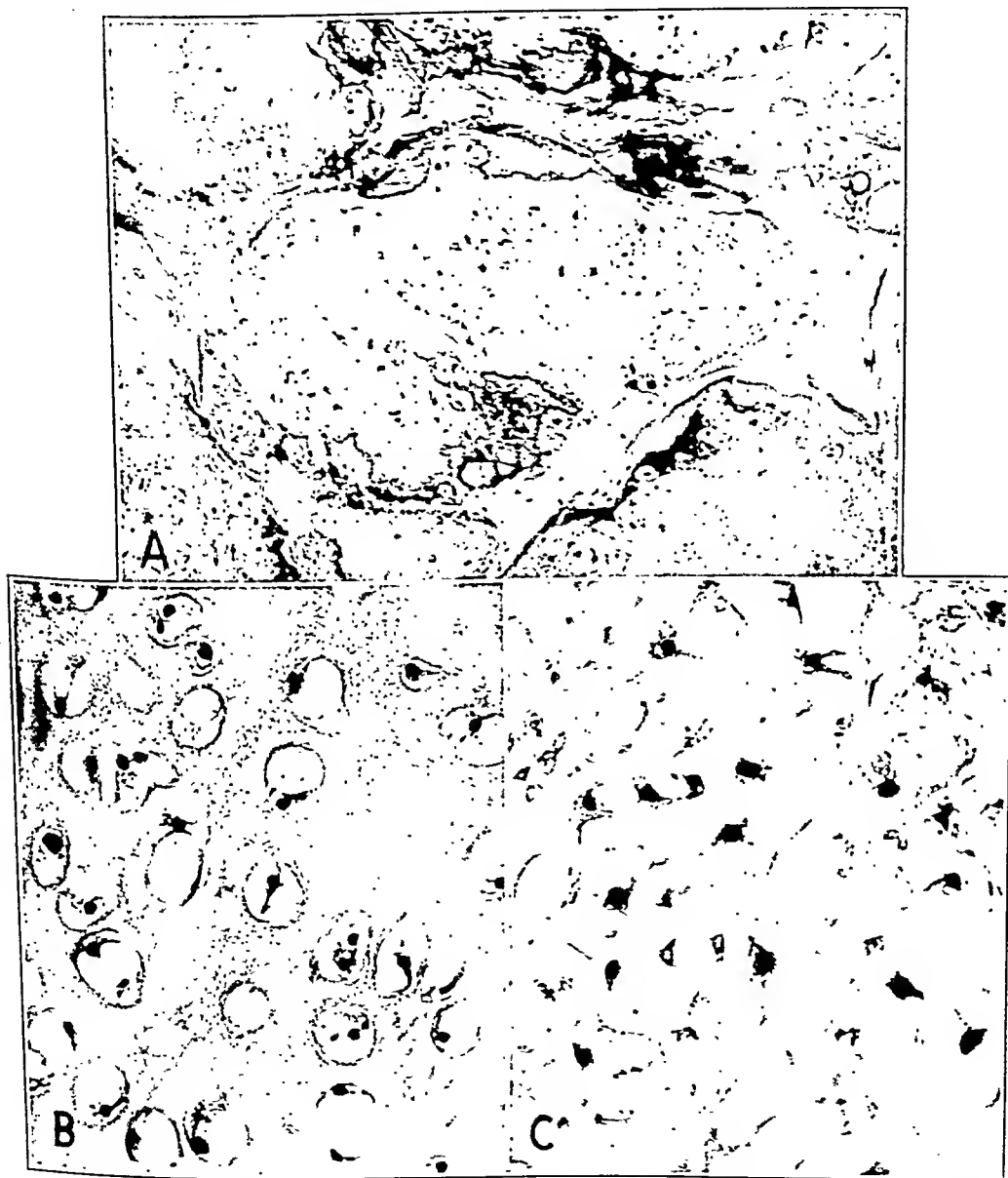


Fig. 3.—Photomicrograph ( $\times 80$ ) showing the architecture of the lobules of cartilage, which in this section are undergoing calcification and ossification, especially about the periphery. (This tissue represents some of the less heavily calcified cartilage curetted from the lesion illustrated in figure 2 E.) B, photomicrograph ( $\times 240$ ) showing hyaline cartilage the cells of which are surrounded by lacunas. C, photomicrograph ( $\times 240$ ) showing cartilage whose intercellular material is edematous and mucoid and whose cells no longer lie in clearcut lacunas. Note that in both A and B there seem to be no binuclear cells and the cell nuclei are relatively small (compare with figure 4 C and D, which are from chondrosarcomas).



bits of dull white cartilage and yellowish, definitely gritty tissue representing heavily calcified and even ossified cartilage. On the other hand, the curettings from still other lesions may consist mainly of obviously calcified and ossified cartilage and may be only meagerly interspersed with islands of hyaline cartilage.

Calcification, and also ossification, of a chondroma is best interpreted as a process of regression or aging or even of healing. In our cases it was more pronounced, on the whole, in the lesions involving long bones, especially of adults. It was also moderately pronounced in some of the lesions in phalangeal and metacarpal bones, especially of the middle-aged adults. Apparently it can be induced artificially by intense irradiation of the lesion.

Microscopically, too, the tendency of the cartilage tissue to be divided off into fields or lobules (fig. 3 *A*) is of course apparent, though more so in some specimens and in some areas than in others. Frequently the facets of cartilage are separated by clefts, and it is not difficult to deduce from comparison of different fields the course of evolution of these spaces. They are formed at sites of swelling and fusion of cartilage cell lacunas associated with disintegration of the cells within. Eventually many of the spaces thus created are invaded by blood vessels. If the cartilage immediately bordering on the spaces becomes calcified or ossified, the space may even come to contain some fatty and myeloid marrow. Furthermore, the individual benign enchondromas vary in respect to cellularity. Some are rather rich in cells; others are relatively poor, and still others show intermingled richly and poorly cellular areas.

In part or throughout, the intercellular ground substance may be hyaline. When it is, the cells, as a rule, lie in lacunas, many of which may be fairly large, and a lacuna does not usually contain more than one cell, though some lacunas show two and an occasional one may show even a nest of cells (fig. 3 *B*). In some areas the intercellular substance may appear edematous or even mucoid, and where it does the cartilage cells tend no longer to be surrounded by lacunas and their cytoplasm is found multipolar or stellate (fig. 3 *C*). Apparently an early stage of this regressive process is represented by unmasking of the collagen fibers and an acidophilic-staining tendency of the ground substance.

In sections stained with hematoxylin, such ground substance as is undergoing calcification will at least look dusty, in consequence of the presence of calcareous granules in it (fig. 4 *A*). When the calcification is more pronounced, the granules may be particularly conspicuous around lacunas and also at the periphery of the cartilage lobules, especially where the latter border on interlobular vascular spaces. Where the calcareous status is clearly pronounced, the cartilage cells may be found to have undergone necrobiosis or even to have disappeared completely (fig. 4 *B*). Heavily calcified areas, especially where they border on the vascular spaces, may even undergo ossification by process of metaplasia.

In attempting to evaluate the benignity of a cartilage tumor, one should concentrate on the cellular elements and specifically on those in the viable and not too heavily calcified areas. Also, one should avoid tissue from the immediate sites of fractures. In representative areas the cartilage cells of a clearly benign enchondroma will be found consistently small. Their cytoplasm is pale and often more or less vacuolated, and its outlines are frequently indistinct. Their nuclei, too, are consistently small and are roundish and dark staining. Indeed, practically all of the cartilage cells of a benign enchondroma present essentially this appearance, whether or not they lie in lacunas and irrespective of the size of the latter if they do. Scanning many preserved fields from as many parts of the lesion as possible, one may find cartilage cells which, though small, contain two nuclei. However, some lesions show practically no cells of this kind, while in others most of the

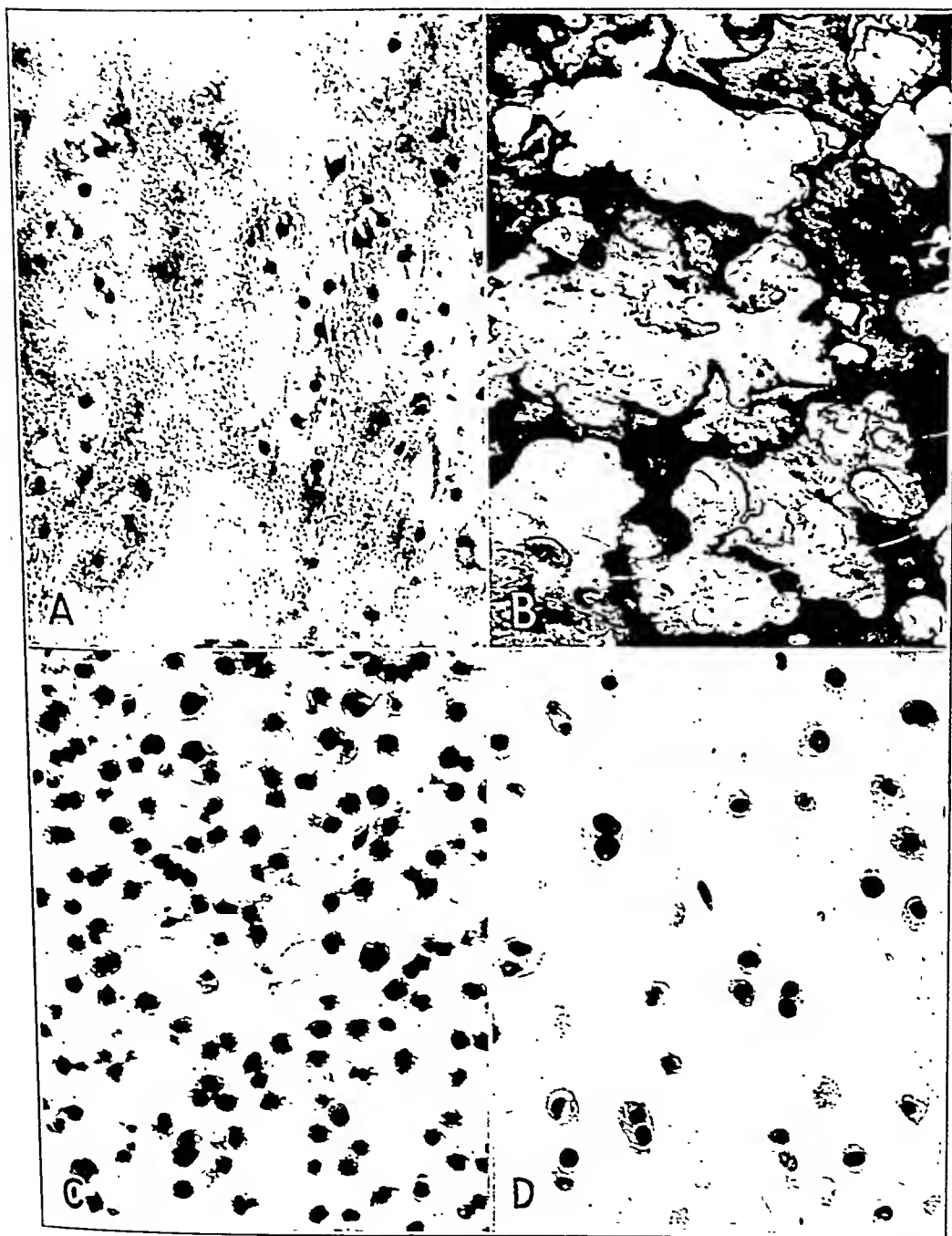


Fig. 4.—*A*, photomicrograph ( $\times 240$ ) showing heavy calcareous dusting of the intercellular material of the cartilage. *B*, photomicrograph ( $\times 76$ ) showing an area of heavily calcified cartilage. *C*, photomicrograph ( $\times 240$ ) from a chondrosarcoma the cytologic structure of which is not yet crudely and obviously sarcomatous. *D*, photomicrograph ( $\times 250$ ) from another chondrosarcoma of the same kind. However, note that in both *C* and *D* the nuclei are plump, and many of the cells have plump double nuclei. Compare these illustrations with those of benign cartilage growths shown in figures 3 *B* and *C* and 4 *A*.

fields will show none, but an occasional field will show one or two or even several. Such binuclear cartilage cells are cells in process of amitotic division, and a clearly benign enchondroma does not show cartilage cells in mitosis.

Altogether, then, solitary benign enchondromas of bone vary in respect to degree of cellularity, distribution of the cells, presence or absence of lacunas about the cells and amount and character of the ground substance between the

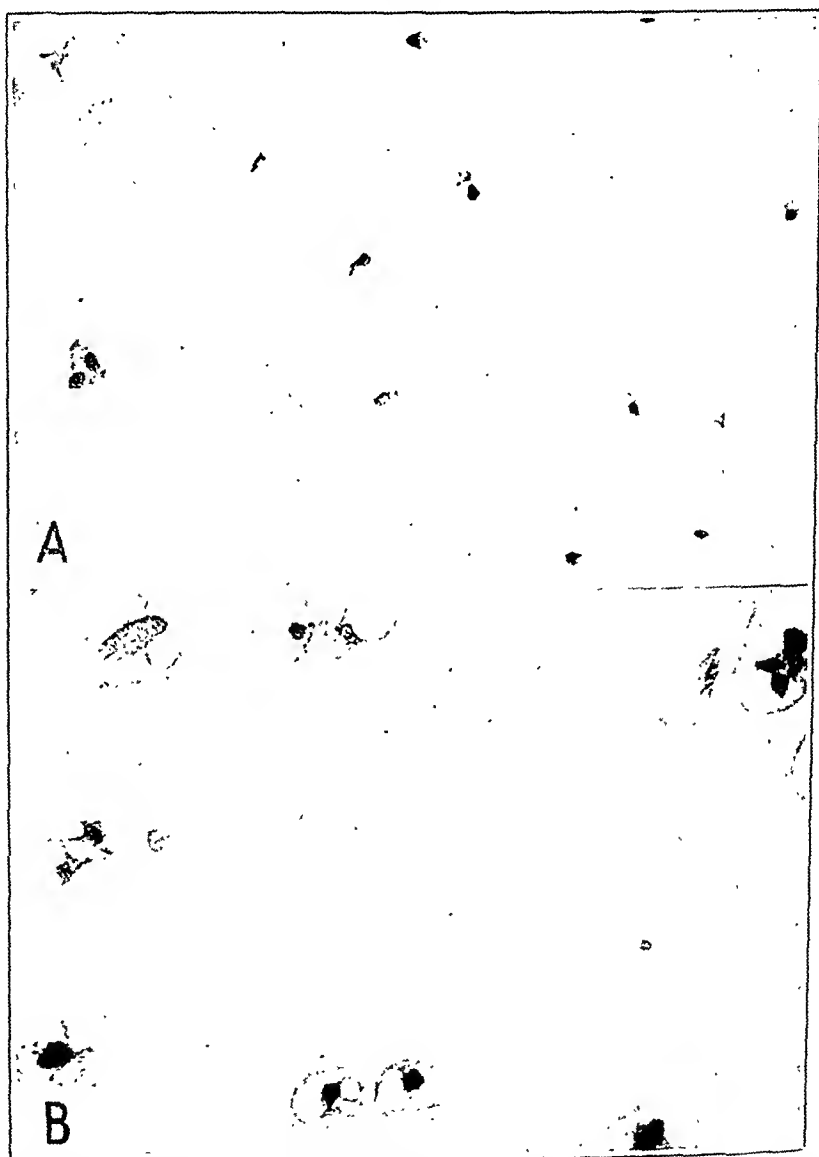


Fig. 5.—*A*, photomicrograph ( $\times 240$ ) of biopsy material obtained from the lesion shown in figure 2*F*. Note that there is only one cell containing two nuclei and furthermore that these nuclei, as well as all the other nuclei shown, are small. Compare this with the photomicrographs of other benign enchondromas (figs. 3*B* and *C* and 4*A*) shown under the same magnification. *B*, photomicrograph ( $\times 240$ ) showing a field from the same case as that represented by *A*, but taken ten months later and specifically from the presection specimen. Fields like it were found only here and there among the sections. Note the change in the character of the cells, in particular the presence now of cells with giant nuclei and multiple nuclei and the plumping of the nuclei even in the uninuclear cells.

cells. What stamps the lesion as benign cytologically is the fact that the viable cartilage cells are rather small and their single nuclei definitely not plump.

While one does find, here and there, some cells (still small) with two nuclei, one does not find them regularly in all fields, even in small numbers. (See, for instance, figures 3 *B*, 3 *C* and 4 *A*, and compare with figures 4 *C* and 4 *D*, all of which represent the same magnification.)

As already noted, benign enchondroma (especially in a long tubular bone) sometimes undergoes malignant transformation. As a benign growth, the lesion may have been present for many years and may even have been entirely symptomless until there was a change in its nature. Prior to its revivescence and malignant transformation, the enchondroma may even have become extensively calcified and ossified. The evolution of a chondrosarcoma out of a benign enchondroma, though sometimes rapid, is usually an extremely slow process. Early in this evolution, cytologic evidence of change in the direction of malignity is already present.<sup>1a</sup> However, at this stage, as we have shown more fully elsewhere,<sup>1</sup> the significant cytologic aberrations are by no means obvious and furthermore are usually present only in scattered fields. To recognize them, one has to take due cognizance of the characteristic cytologic pattern of the benign lesion as described and watch for such deviations from that pattern as the presence of more than an occasional binuclear cell and a general plumping-up of the nuclei. If one finds, even if only in scattered areas, many microscopic fields showing several or more binuclear cartilage cells, or many cartilage cells with plump nuclei, and especially any cartilage cells containing large or multiple nuclei, the growth is no longer a clearly benign enchondroma. It may not be until much later, however, that the histologic picture of the lesion is that of a crudely obvious chondrosarcoma.

In a pertinent case<sup>10</sup> in which the upper end of a humerus was involved, the initial surgical intervention was removal of tissue for biopsy, which seemed to confirm the clinical diagnosis of a calcifying and ossifying enchondroma (fig. 2 *F*). However, after the removal of tissue the patient experienced increasing pain in the affected area and increased loss of function, and it was evident from comparative roentgen examinations that the lesion was growing, slowly but steadily. For these reasons, ten months after the operation the upper end of the humerus was resected and the defect filled in by insertion of a substantial portion of the upper end of a fibula. Reexamination and comparison of the biopsy and resection specimens (figs. 5 *A* and 5 *B* respectively) leave no doubt that one was dealing with a chondrosarcoma in the early stages of its evolution out of a benign enchondroma. However, the patient has shown no recurrence during the subsequent four and one-half years.

#### TREATMENT AND PROGNOSIS

In general, the treatment of choice for solitary benign enchondroma of bone is surgical. It consists specifically of curettement, perhaps followed by chemical cauterization and, in addition, under appropriate circumstances, collapse of the distended part of the cortical wall and introduction of bone chips or insertion of a solid bone graft. Of the 14 phalangeal lesions, some were merely curetted, some were curetted and cauterized and some were curetted and filled with bone chips, sometimes after and sometimes without cauterization. No recurrences were noted in any of these cases, and healing was prompt and uncomplicated in all of them except 1. In that case, a course of preoperative irradiation therapy had been given. The precise dosage which was used is not known to us, but the

10. Burack, P. I.: Ossifying Enchondroma of Head of Humerus. Bull. Hosp. Joint Dis. 1:3 (March) 1940.

patient stated that she had received "10 x-ray treatments of the lesion, without benefit." After the operation, the wound suppurated slightly and a number of the bone chips which had been inserted were sequestered. One cannot, of course, be sure that this complication was ascribable to the preoperative irradiation, but that, in general, heavily irradiated lesions in bone subsequently operated on are particularly susceptible to infection is well known.

Of the 6 lesions in metacarpal and metatarsal bones, 5 were likewise treated by curettement, collapse of the cortical wall and introduction of bone chips or a solid graft. In these cases, too, the postoperative course seems to have been uniformly favorable and apparently there were no recurrences. The exception noted was the case in which the entire metacarpal bone was extirpated, apparently because of the extensiveness of involvement of this bone. No follow-up is available in this case, but anatomically the lesion was clearly an entirely benign one.

The same principles of treatment were followed in regard to 5 of the 8 lesions of long tubular bones, again with uniformly good end results. Of the other 3, 1 (a femoral lesion) was treated (elsewhere) by resection of the lower end of the affected bone. Such treatment is obviously too radical for a solitary benign enchondroma, though the surgeon may have felt that by being drastic he was forestalling malignant transformation of the lesion. As to the other 2, removal of tissue for biopsy constituted the original surgical intervention in 1 of them,<sup>11</sup> while in the other (as previously noted) a biopsy was followed ten months later by resection of the affected upper end of the humerus, since in the interval the lesion showed clinical progression in the direction of malignancy.

#### SUMMARY AND CONCLUSIONS

The clinical (including therapeutic), roentgenographic and pathologic aspects of solitary benign enchondroma of bone have been described on the basis of 28 cases from our files. As its name implies, the lesion is a benign cartilaginous growth which develops in the interior of an affected bone and involves only a single bone in any 1 subject. The lesion has a definite predilection for bones of the limbs, particularly the phalanges of the fingers, the metacarpal bones, the humerus and the femur.

In relation to tubular bones, the lesion starts its development within the shaft and apparently within a metaphysial region in particular. It may come to involve a considerable portion of the shaft. On the other hand, it may extend into the adjacent or nearer epiphysis, though it is not likely to do this until after the epiphysis has fused with the shaft. In the course of its development, the lesion may remain strictly confined within the interior of the bone without bulging out the cortex anywhere. More often, however, it thins and distends the cortex, creating a bulge which can be detected even clinically.

Apparently the lesion is not more common in one sex than in the other. Though the great majority of the patients are adolescents or young or middle-aged adults when presenting themselves for treatment, the lesion seems usually to be already of long standing at that time. The clinical complaints are generally mild. Usually swelling has been noted in the affected part, and there may be

11. In this case, the lesion, in the upper end of the humerus of a man of 52 years, appeared to be a heavily calcified and ossified enchondroma. The biopsy tissue already revealed microscopically some scattered groups of cartilage cells with plump nuclei, so that when we restudied the slides in connection with the writing of this paper we were aware that this enchondroma possessed aggressive qualities. Several weeks after this manuscript was submitted for publication, the patient returned with a frank chondrosarcoma. There had been an interval of twelve months between the diagnostic biopsy and the resection of the upper end of the humerus on account of the obvious chondrosarcoma which had developed in the meantime.

some pain and tenderness as well, especially when trauma has induced infraction of the distended cortex.

The roentgenogram is a valuable guide in the diagnosis of solitary benign enchondroma. In relation to enchondromas in long tubular bones, the presence of radiopaque dots or even blotches representing foci of calcification and ossification often enables one to make the correct diagnosis even when the roentgenographic appearance of the lesion is otherwise ambiguous. In relation to phalanges and metacarpal and metatarsal bones, the chances are strong that one is dealing with an enchondroma if a fairly large area of rarefaction associated with thinning and bulging of the cortex is seen. This is true even in the absence of spotty calcification, just on the basis of the relative commonness of the lesion in these bones.

The ultimate decision as to whether a central cartilaginous growth in bone is benign must be based on the cytologic findings. The picture of benignity is created by the character of the cells (as observed in viable and not too heavily calcified areas of the lesion) and specifically by the following features: (1) The vast majority of the cartilage cells have only one nucleus; (2) this nucleus tends strongly to be rather small and definitely not plump in relation to the cell as a whole; (3) such cells as are binuclear are still small, still have small (and not plump) nuclei and are found only occasionally and even then only in scattered fields.

An enchondroma, especially of a long tubular bone, may undergo malignant transformation. Cytologically, in the early stages of this transition the lesion will deviate from the benign pattern just sketched, at least in showing in scattered fields many cells with plump nuclei, more than an occasional cell with two such nuclei and even some giant cartilage cells with large single or multiple nuclei.

In connection with the management of solitary benign enchondroma, good end results are to be expected from conservative surgical intervention.

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# PRIMARY CARCINOMA OF THE INFRA-AMPULLARY PORTION OF THE DUODENUM

WITH EXAMPLE OF PROBABLE ORIGIN FROM ABERRANT PANCREATIC TISSUE

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Primary carcinoma of the duodenum is usually classified according to its relation to the ampulla of Vater as supra-ampullary, periampullary and infra-ampullary. In any of these situations, carcinoma of the duodenum is rare. In a series of 350,286 autopsies, Eger<sup>1</sup> found an incidence of 0.033 per cent. According to Hoffman and Pack,<sup>2</sup> carcinoma of the duodenum constituted 0.3 per cent of all intestinal carcinomas, while Eger<sup>1</sup> stated that 45.6 per cent of carcinomas of the small intestine are found in the duodenum. Of these, 24.9 per cent were supra-ampullary, 61.9 per cent were periampullary and 13.1 per cent were infra-ampullary.<sup>2</sup> If carcinomas arising from the ampulla and papilla of Vater, which should be classified as tumors arising from the biliary tract, are excluded, the percentage of tumors arising in the periampullary portion approximates that of growths arising in the supra-ampullary portion.<sup>3</sup>

In 1937 Lieber, Stewart and Lund<sup>4</sup> in a critical review of the literature found 62 cases of carcinoma of the infra-ampullary portion of the duodenum. However, they were able to accept as authentic only 28 cases, since in the remainder insufficient data had been given to establish the diagnosis. They described 2 new instances of carcinoma of the infra-ampullary portion of the duodenum. Since that time there have been reported 5 additional cases,<sup>5</sup> in only 3 of which was there a postmortem examination.<sup>6</sup>

The clinical features and the gross and microscopic appearance of carcinoma of the duodenum have been fully described in other papers<sup>7</sup> and will be referred

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1. Eger, S. A.: Primary Malignant Disease of Duodenum, *Arch. Surg.* **27**:1087 (Dec.) 1933.

2. Hoffman, W. J., and Pack, G. T.: Cancer of Duodenum, *Arch. Surg.* **35**:11 (July) 1937.

3. Harbin, W. P.; Harbin, W. P., Jr., and Harbin, L.: *Ann. Surg.* **101**:961, 1935.

4. Lieber, M. M.; Stewart, H. L., and Lund, H.: Carcinoma of Infrapapillary Portion of Duodenum, *Arch. Surg.* **35**:268 (Aug.) 1937.

5. (a) Bergendal, A.: *Acta radiol.* **20**:417, 1939. (b) Claiborn, L. N., and Dobbs, W. G. H.: *Surgery* **4**:97, 1938. (c) Macindoe, P. H.: *M. J. Australia* **1**:48, 1940. (d) Pollock, S.: *Radiology* **31**:362, 1938.

6. Bergendal.<sup>5a</sup> Claiborn and Dobbs.<sup>5b</sup> Macindoe.<sup>5c</sup>

7. (a) Eusterman, G. B.; Berkman, D. M., and Swan, T. S.: *Ann. Surg.* **82**:153, 1925. (b) Mateer, J. G., and Hartman, F. W.: Primary Carcinoma of Duodenum, *J. A. M. A.* **99**:1853 (Nov. 26) 1932. (c) Meyer, J., and Rosenberg, D. H.: Primary Carcinoma of Duodenum, *Arch. Int. Med.* **47**:917 (June) 1931. (d) Eger.<sup>1</sup> (e) Hoffman and Pack.<sup>2</sup> (f) Lieber, Stewart and Lund.<sup>4</sup>

to only briefly. The patient complains of epigastric distress, usually aggravated by food and relieved by vomiting. Nausea is usually associated with the vomiting, and as the condition progresses the vomiting becomes more frequent. In the cases of infra-ampullary carcinoma, the vomitus contains bile. In addition to these symptoms, there is anorexia with loss of weight going on to cachexia. Patients often complain of attacks of diarrhea alternating with attacks of constipation. Examination of the stools may show the presence of occult blood. A mass in the epigastrium may be noted. The duration of the illness from the onset of symptoms is from three to eighteen months, with an average of seven months. Of 30 patients with carcinoma of the infra-ampullary portion of the duodenum whose cases were reviewed by Lieber, Stewart and Lund<sup>4</sup> 20 were men ranging in age from 40 to 74 years and averaging 58 years, while 10 were women with an age range of 35 to 61 years and an average age of 48 years.

In relatively few of the published cases of primary carcinoma of the duodenum has the condition been diagnosed roentgenologically. In contrast to the pathologic descriptions, the roentgen findings regarding the duodenum have been variously reported as normal, or as due to pyloric obstruction. On the occasions when a definite localization of the lesion has been accomplished, the defect usually has been ascribed to extrinsic pressure or to an invasive process from some extrinsic lesion. Rarely has an intrinsic lesion of the duodenum been considered.

Carman<sup>8</sup> believed that cancer of the supra-ampullary area could not be differentiated roentgenologically from ulcer. The serrated appearance of the second and third portions of the duodenum normally produced in the barium pattern by the valvulae conniventes and the commonly rapid motility in that area make the diagnosis of early cancer in these areas difficult in the absence of obstruction. Shanks<sup>9</sup> stated: "In these cases there is a considerable tendency to obstructive ileus. . . . Radiographically a duodenal ileus is evident and possibly a filling defect from the obstructing growth." In a recent paper, Bergendal<sup>5a</sup> commented that the difficulty in recording and correctly diagnosing primary duodenal cancer is due to the position of the duodenum and its close proximity to adjacent organs.

Roentgenologic examinations were performed in 18 of the 30 cases collected by Lieber, Stewart and Lund.<sup>4</sup> In only 6 of the 18 was the lesion correctly located.<sup>10</sup> The several roentgenologists had considered that the lesions were due to adhesions, pressure defects from an intrinsic tumor or pressure defects from mesenteric vessels. In some instances, no opinion was recorded. It was only on the third examination in Bergendal's first case that a roentgenologic diagnosis of primary duodenal cancer was given. Hellmer<sup>11</sup> thought that the demonstrated intraluminal defect in Bergendal's second case might be due to either a primary carcinoma of the duodenum or an invasion of the duodenum by a carcinoma of the pancreas.

Pathologically, carcinoma of the duodenum may be either of the scirrhous, annular type composed of firm, dense white tissue or of the soft, polypoid, pedunculated, medullary type. Ulceration is common. Stenosis with complete or almost complete occlusion of the lumen of the bowel, dilatation of the stomach and the proximal portion of the duodenum and compensatory hypertrophy of the walls

8. Carman, R. D.: *The Roentgen Diagnosis of Diseases of the Alimentary Tract*, ed. 2, Philadelphia, W. B. Saunders Company, 1920.

9. Shanks, S. C.; Kerley, P., and Twining, E. W.: *A Text-Book of X-Ray Diagnosis*, London, H. K. Lewis & Co., Ltd., 1938, vol. 2.

10. Fariñas Mayo, L.: *Bol. Liga contra el cáncer* 9:210, 1934. Lundberg, S.: *Acta chir. Scandinav.* 56:417, 1924. Kellogg, E. L.: *The Duodenum*, New York, Paul B. Hoeber, Inc., 1933. Pauchet, V., and Luquet: *Bull. Acad. de méd., Paris* 97:276, 1927. Sala, A. M.: *Radiology* 25:437, 1935. Mateer and Hartman.<sup>7b</sup>

11. Hellmer, cited by Bergendal.<sup>5a</sup>



are among the most striking gross features. The tumors infiltrate the adjacent retroperitoneal tissue and the contiguous parts of the pancreas. The common sites of metastases are the regional lymph nodes and the liver, while occasionally the lungs, bones and peritoneum are involved. However, metastases are said to occur late in the course of the disease. Among the 30 cases collected by Lieber, Stewart and Lund<sup>4</sup> ulceration of the tumor was present in 16, the growth was completely annular in 19 and obstruction was complete or almost complete in 17. The scirrhous type of tumor was the commonest. Metastases occurred in 50 per cent of the cases.

Histologically, the tumors are of a cylindric cell type; in some instances the cells are well differentiated and in others extremely anaplastic. They may be columnar or cuboidal, with the usual neoplastic characteristics, and occur in solid nests or in acinar formation. The annular tumors have abundant stroma with few cells, while

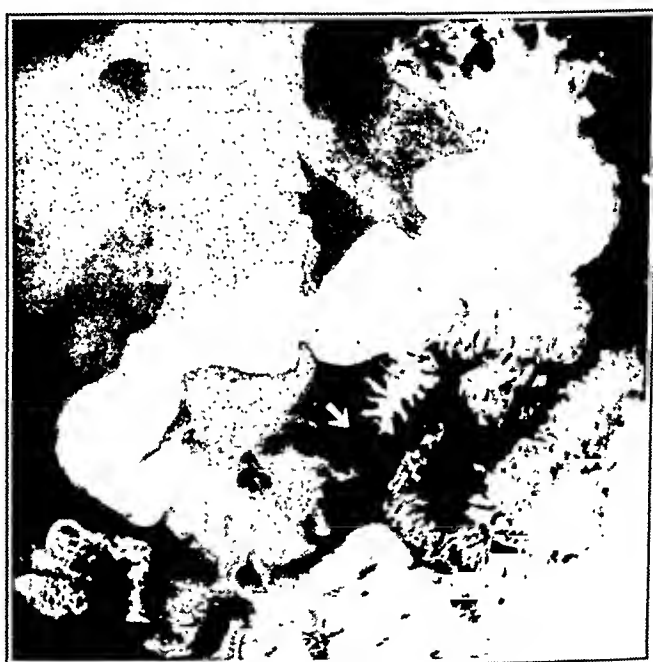


Fig. 1.—Roentgenogram showing marked dilatation of the duodenum proximal to an area of narrowing (indicated by arrow) which involves the third part of the duodenum. The gastric outline is normal.

the medullary lesions have scant stroma with abundant cells. The tumors in which ulceration has occurred show inflammatory changes.

The following case of primary carcinoma of the infra-ampullary portion of the duodenum is reported because of the rarity of the condition, because it demonstrates the possibility of reaching a correct clinical diagnosis by means of careful roentgenologic examination and because it illustrates the possibility of origin of carcinoma of the duodenum from aberrant pancreatic tissue.

#### REPORT OF A CASE

W. J., a 35 year old Polish man, was admitted to the Royal Victoria Hospital with the following history:

He was a restaurant worker, a heavy smoker and drinker. He was in his usual good health until six months before admission to the hospital, when he began to have attacks of epigastric pain coming on late after meals and relieved by food. These symptoms progressed. One month before admission, he began to complain of constipation and failing appetite with loss of weight and strength. One week before admission he started to vomit with increasing

frequency, up to five or six times daily, and even after taking fluids. He then consulted a physician for the first time and was admitted to the hospital.

The physical examination revealed a thin man showing evidence of recent loss of weight. The abdomen was diffusely tender, but no abdominal mass was palpable. There was a non-tender, firm, nodular mass palpable in the anterior wall of the rectum and fixed to the surrounding tissues. Small subcutaneous nodules were present over the whole body but were most numerous on the left thigh and the right side of the neck. The gastric juice contained no free hydrochloric acid, and the total acidity was from 20 to 40. The hemogram showed 5,400,000 red blood cells, 7,900 white blood cells and a hemoglobin content of 100 per cent.



Fig. 2.—*A* and *B*, serial roentgenograms taken with local compression. The ulcer crater is shown overlying the left superior margin of the body of the third lumbar vertebra. *C*, roentgenogram showing concentric narrowing of the duodenal lumen distal to the ulcer and dilatation of the second portion of the duodenum proximal to the ulcer.

The fragility of the red blood cells was normal and the sedimentation velocity and the prothrombin time were slightly prolonged. There was no hyperbilirubinemia.

On roentgen examination (figs. 1 and 2) there was found just distal to the junction of the second and third portions of the duodenal loop a definite narrowing with irregularity of the lumen of the duodenum. Only a small channel just proximal to the duodenojejunal junction permitted barium to pass to the jejunum with the persistence of a fleck of barium having the appearance of opaque material retained in an ulceration. Extreme tenderness to palpation was present over this region. Four hours later 60 per cent of the barium meal

remained in the stomach. The opinion of the roentgenologist was: "The zone of deformity and irregularity and narrowing, involving the distal portion of the duodenal loop, is due to an intrinsic lesion of the duodenum, probably neoplasm, with an ulcerated area in this zone."

Eleven days after the patient's admission to the hospital an exploratory laparotomy was done by Dr. J. C. Armour, who found a large tumor mass involving the duodenum at the duodenojejunal junction. There were numerous metastases to the parietal peritoneum and along the mesenteric attachment of the small intestine. A biopsy of a nodule in the omentum showed adenocarcinoma. The vomiting persisted, and the patient's condition became progressively worse. He died four weeks after operation, or about seven and a half months after the onset of symptoms.

*Postmortem Examination.*—A complete autopsy was performed four hours after the patient's death. In the following summary only the observations pertaining to the duodenal tumor will be described.

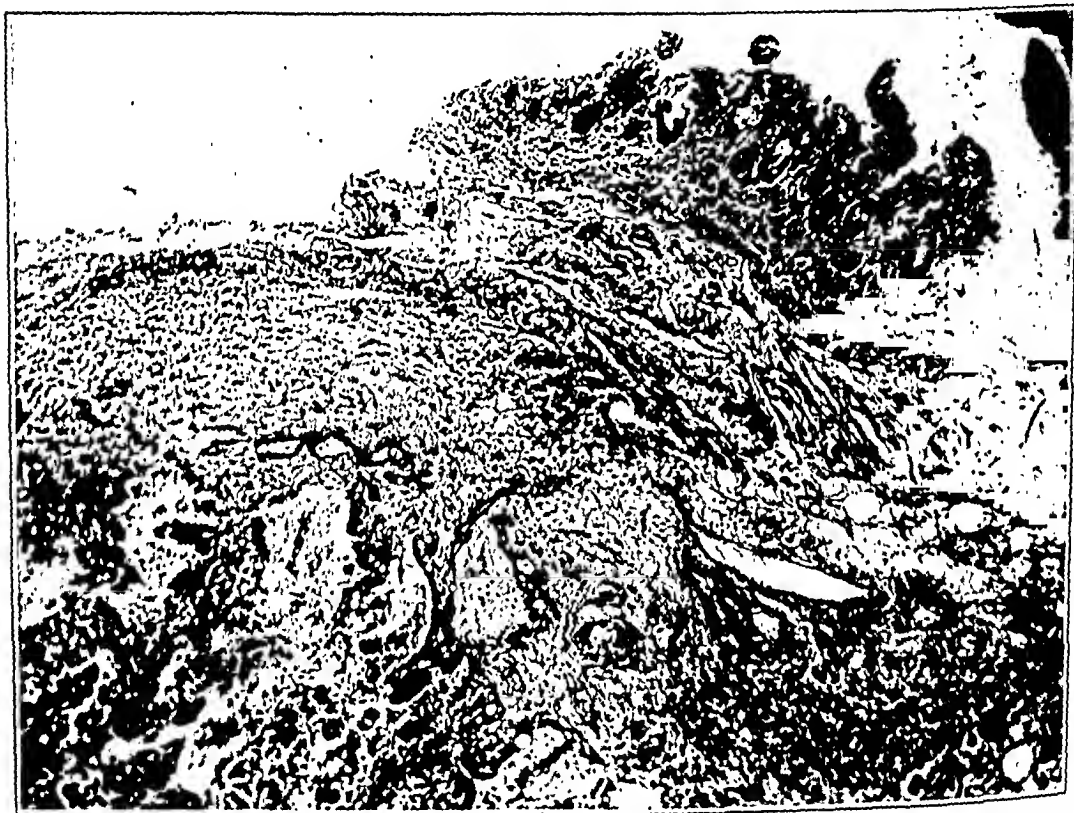


Fig. 3.—Photomicrograph showing microscopic appearance of the margin of the duodenal ulcer. Note the abrupt termination of duodenal mucosa which is essentially normal in structure and has no connection with the mass of tumor tissue in the submucosa.

In the duodenum, a firm nodular mass measuring 6 by 4 cm. was found almost completely encircling the infra-ampullary portion, infiltrating the adjacent fatty tissue and displacing the pancreas superiorly. Examination of the lumen of the duodenum revealed a deep ulcerated area with a soft necrotic base and overhanging edges about 1.5 cm. distal to the ampulla of Vater, in the superior aspect of the duodenum. Just distal to this, the tumor mass bulged into the lumen but the covering mucosa was intact, though hemorrhagic. The bulging mass produced almost complete obstruction of the duodenum for a distance of 2.5 cm. The cut surface of the tumor was firm and was mottled yellow and gray with small hemorrhagic areas. The duodenal wall was thickened by tumor tissue which appeared to have spread beneath the mucosa. The uncinate process and adjacent parts of the head of the pancreas were displaced rather than invaded by the tumor, as indicated by a distinct line of demarcation between tumor and pancreatic tissue. The stomach and the proximal portion of the duodenum were markedly distended and the walls thickened by hypertrophy of the muscle coats. Along the mesenteric border of the small intestine were small, firm, white metastatic tumor nodules.

These in some areas involved the muscular coat, but the mucosa was everywhere intact. The peritoneal surfaces of the rectovesical pouch, the right lumbar gutter, the inferior aspect of the right side of the dome of the diaphragm and the greater omentum were studded with tumor nodules.

*Microscopic Examination.*—Histologic sections of the duodenal wall including the area of ulceration showed a large mass of tumor tissue which lay chiefly in the submucosa. The

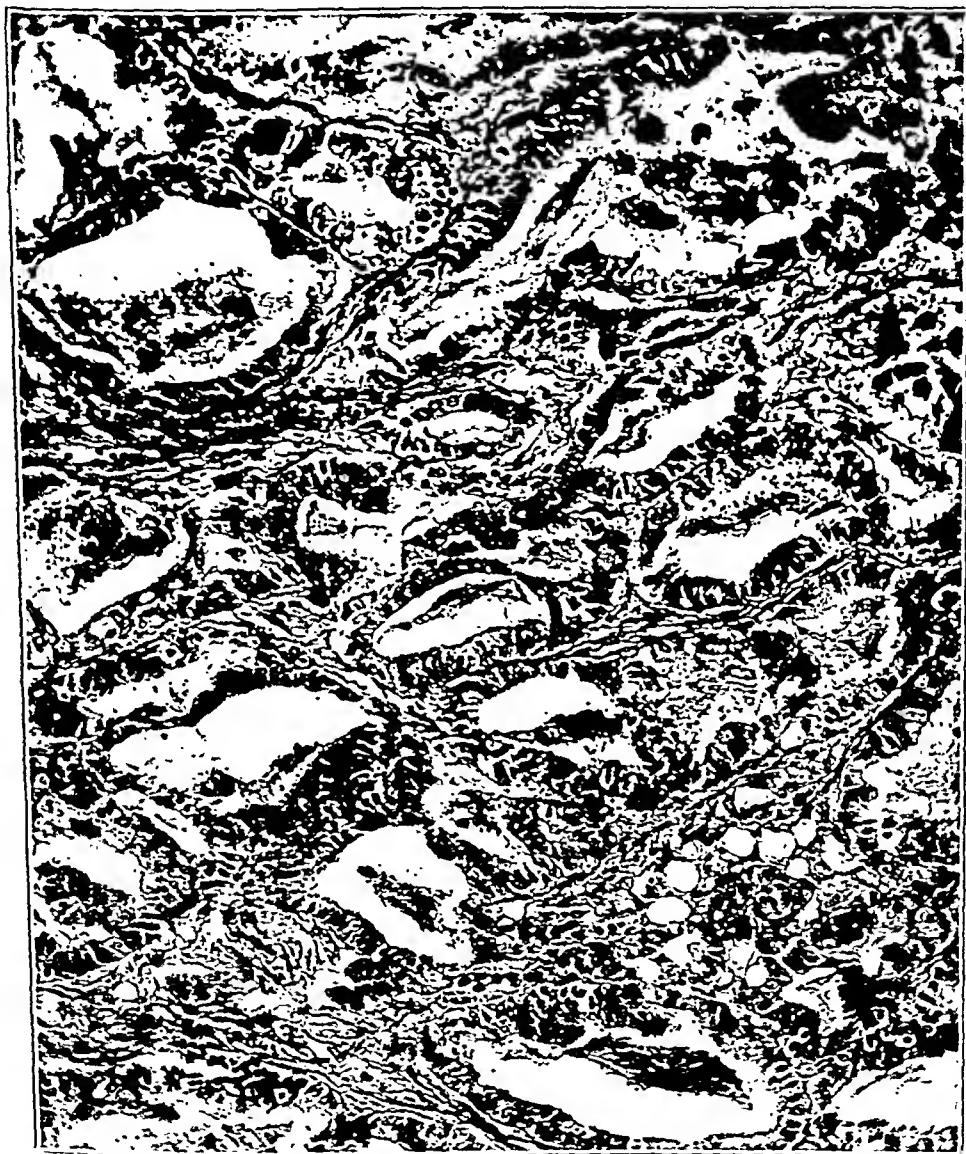


Fig. 4.—Photomicrograph showing the histologic structure of the tumor. The formation of ductlike spaces lined by cuboidal or columnar epithelium is a prominent feature. Several papillary ingrowths of the lining cells are shown. In most areas the stroma was much more abundant than in this field.

submucosal layer of tumor was deepest in the region just distal to the ulcer, but a thinner layer of neoplastic tissue was present in the base of the ulcer and spread through the submucosa for a considerable distance in all directions. The duodenal mucosa was elevated by the tumor, but it was not at any point connected with the tumor tissue and apart from some hemorrhagic extravasations it was relatively normal in appearance. At the margins of the

ulcer the mucosa was interrupted abruptly and showed no neoplastic or hyperplastic changes and no continuity with the underlying tumor cells (fig. 3). The tumor tissue, apart from a few small solid clusters and strands of tumor cells, was composed of many ductlike structures of varying size and shape, lined by cuboidal or columnar epithelial cells which in some areas were thrown up into irregular papillary folds. Their cytoplasm was acidophilic; the nuclei varied greatly in size, shape and depth of staining. Mitotic figures were present in small numbers. The fibrous stroma was moderate in amount. Altogether, the histologic structure was similar to that of a pancreatic carcinoma of duct cell type (fig. 4). The tumor had extended between the muscle bundles and beyond the muscle coats of the duodenum into the peripancreatic fat. The mass of tumor tissue came into immediate contact with the pancreas but was sharply demarcated from it throughout much the greater part of the area of contact. A slight degree of invasion of individual pancreatic lobules was demonstrable in only a few microscopic areas (fig. 5). In the mass of tumor tissue which lay nearest the pancreas careful search failed to reveal any evidence that pancreatic tissue had been replaced by tumor. The tumor mass in this region contained no remnants of normal pancreatic ducts, acini or



Fig. 5.—Low power photomicrograph showing the retroperitoneal tumor mass (above) impinging on the pancreas (below). The line of demarcation between the two is distinct throughout most of this field, although one pancreatic lobule is slightly infiltrated by the tumor.

islets of Langerhans. Thus, while the histologic structure of the tumor suggested an origin from pancreatic tissue, no evidence could be obtained from either the gross or the microscopic examination that it had originated in the pancreas itself. On the contrary, both the gross and the microscopic features of the tumor indicated an origin in the wall of the duodenum, but the structure was not that of a tumor originating from intestinal mucosa. This anomalous situation could be explained only by assuming that the tumor originated from aberrant pancreatic tissue in the duodenal wall.

The metastatic nodules showed neoplastic epithelial cells identical in character with those of the primary growth, but duct formation was rather more conspicuous in the metastases. The subcutaneous nodules were neurofibromas.

The diagnosis was: primary carcinoma of the infra-ampullary portion of the duodenum; secondary carcinoma of the omental and mesenteric lymph nodes, retroperitoneal fat (peripancreatic) and peritoneum; emaciation; acute bronchopneumonia; multiple neurofibromatosis; arteriosclerosis of aorta and coronary arteries (minimal).

## COMMENT

The case of carcinoma of the infra-ampullary portion of the duodenum here reported conformed in the main to the typical clinical history as outlined in the introduction of this paper. There was epigastric distress with anorexia, persistent vomiting and rapid loss of weight. However, no epigastric mass was palpable at any time during the course of the illness, which was of seven and one-half months' duration.

The roentgenologic features in our case were entirely typical. There was an irregular filling defect involving the third portion of the duodenum with a concentric narrowing of the duodenal lumen and dilatation of the duodenum proximal to the area of narrowing. The normal pattern of the valvulae conniventes was obliterated in the area of the filling defect. A localized collection of barium lay in a large ulcer crater in the area of defect without evidence of any sinus tract passing external to the duodenal lumen. Moreover, the tenderness on palpation corresponded in position to the visualized abnormalities.

A number of other pathologic entities may exhibit roentgenologic abnormality which could simulate the evidence in this case in one or more respects. Invasion of the duodenal walls by a carcinomatous extension from the pancreas would be difficult to differentiate, but ulceration within the duodenal lumen without sinus tract formation extending external to the lumen would be unusual. Invasion of the duodenum by a carcinoma of the stomach should be differentiated by demonstration of the gastric lesion. Paraduodenal adhesions could cause obstruction with resultant dilatation of the proximal duodenum, but an extensive filling defect with ulceration would not be expected. Similar comment would also apply to the change produced by an unusual overgrowth of the head of the pancreas. A large impacted intraduodenal gallstone, a foreign body or a benign duodenal tumor might cause a local filling defect and a duodenal dilatation, but the duodenal lumen should be widened at the level of the filling defect rather than narrowed, and deep ulceration is not usual. Pressure defects from an extrinsic tumor, without invasion of the duodenal walls, would not produce a concentric narrowing of the lumen, an obliteration of the pattern of the valvulae conniventes or an ulceration within the duodenum. Sarcoma of the duodenum cannot be differentiated from carcinoma by roentgen examination. For these reasons, the opinion was expressed that the gross lesion demonstrated in this case was due to a primary neoplasm of the third portion of the duodenum.

We believe that only by the correct appreciation of the gross pathologic changes seen in the reported cases of primary duodenal cancer and by a painstaking roentgenoscopic search and study of correctly postured roentgenograms can a correct interpretation of the roentgen findings be made. In the first case cited by Bergendal,<sup>5a</sup> it was only at the third examination that the localization of the lesion was accomplished. Then the opinion was offered that the demonstrated gross filling defect with ulceration was consistent with the findings to be expected in cancer of the third portion of the duodenum. The more recent technical improvements of roentgen apparatus, particularly the addition of facilities for making serialographic film studies at the time of fluoroscopic examination, should improve the study of the duodenum in its entirety.

This case presented the gross pathologic features most frequently described as associated with infra-ampullary carcinoma of the duodenum. The tumor was scirrhous and annular in type. It had almost completely occluded the lumen of the duodenum, producing marked dilatation of the stomach and the proximal portion of the duodenum with hypertrophy of their walls. Ulceration was also present.

The histologic structure of the tumor in our case closely resembled that of a duct cell carcinoma of the pancreas. Similar observations in cases of primary carcinoma of the duodenum have been made by others, who have hinted at the possibility that carcinoma of the duodenum may arise from aberrant pancreatic tissue. The occurrence of such aberrant tissue is not uncommon. Faust and Mudgett<sup>12</sup> collected from the literature 369 cases and added 1 case of their own. Their analysis of the distribution of aberrant pancreatic tissue showed that it was located most frequently in the wall of the duodenum (30 per cent), stomach (26 per cent), jejunum (18 per cent) or ileum (13 per cent). Other rarer sites included the gallbladder, spleen, mesentery and omentum. In the last 1,970 autopsies performed in the department of pathology of McGill University, we have found 21 instances of aberrant pancreatic tissue, an incidence slightly greater than 1 per cent. Of these, 17 occurred in the duodenum, 3 in the jejunum and 1 in the stomach.

In spite of the relatively frequent occurrence of aberrant pancreatic tissue, the idea that carcinoma could originate in such pancreatic rests was scoffed at by Bland-Sutton,<sup>13</sup> who stated that there was no evidence to support such a theory. He admitted, however, that pathologists are not devoid of imagination. Nevertheless, the diagnosis of a malignant tumor originating in aberrant pancreatic tissue has been made by no less an authority than W. H. Welch. Jefferson<sup>14</sup> in 1916 reviewed a case in which the pathologic report was made by Professor Welch, who found a malignant adenoma of the pylorus arising in misplaced pancreatic tissue. More recently, Schmidt<sup>15</sup> described an adenoma of pancreatic tissue located in the upper part of the jejunum. Bookman<sup>16</sup> found a disklike tumor in the first portion of the duodenum which had no connection with the pancreas but which on histologic examination proved to be a carcinoma of pancreatic tissue. Vecchi<sup>17</sup> some years ago reported a large islet cell tumor which he described as a malignant adenoma arising in accessory pancreatic tissue located near the tail of the pancreas. Recently, Ballinger<sup>18</sup> reported a case of carcinoma of the pancreas of islet cell type arising in aberrant pancreatic tissue in the liver. Widespread metastases were present but no tumor tissue was found in the pancreas itself.

It is obvious that reports of benign and malignant tumors which have originated in aberrant pancreatic tissue are relatively few. However, there is no reason to doubt that tumors could arise from such misplaced tissue. Indeed, it might be supposed that such aberrant tissue, when it occurs, would be more likely to give origin to neoplasia than would the tissue of the pancreas itself. In the case here reported, there could be no doubt that the tumor arose in the wall of the duodenum, since this was the only structure from which a carcinoma could arise that was actually occupied by the tumor. The uncinate process of the pancreas was displaced rather than replaced by the tumor mass, and between the two there was grossly visible a sharp line of demarcation. It is true that the earliest beginnings of invasion of a few pancreatic lobules were demonstrated microscopically along this line, but apart from this the pancreas was completely free of tumor. On these grounds, the possibility of origin of the tumor from the pancreas as such was abandoned. In the duodenal wall the greatest mass of tumor tissue lay in the

12. Faust, D. B., and Mudgett, C. S.: *Ann. Int. Med.* **14**:717, 1940.

13. Bland-Sutton, J.: *Tr. M. Soc. London* **38**:1, 1914.

14. Jefferson, G.: *Brit. J. Surg.* **4**:209, 1916.

15. Schmidt, H.: *Centralbl. f. allg. Path. u. path. Anat.* **31**:497, 1921.

16. Bookman, M. R.: *Ann. Surg.* **95**:464, 1932.

17. Vecchi, A.: *Arch. per le sc. med.* **38**:277, 1914.

18. Ballinger, J.: Hypoglycemia from Metastasizing Insular Carcinoma of Aberrant Pancreatic Tissue in Liver, *Arch. Path.* **32**:277 (Aug.) 1941.



submucosa, elevating the mucosa, which, however, was intact and essentially normal over a considerable area. The mucosa terminated abruptly at the margins of the area of ulceration without showing any neoplastic or even hyperplastic changes, and there was a definite lack of continuity between the duodenal epithelium and the epithelial cells of the tumor around the margins of the ulcer at all points examined. Not only was the lack of connection between the duodenal mucosa and the tumor mass beneath it inconsistent with the assumption of origin of the latter from the former, but the histologic structure of the tumor was not that of a tumor arising from intestinal mucosa. Its structure was typically that of a duct cell carcinoma of the pancreas. These apparently inconsistent observations could be brought into complete harmony only by the assumption that the tumor arose from aberrant pancreatic tissue in the wall of the duodenum. Indeed, the location, the manner of spread and the gross and microscopic appearance of the tumor were precisely what one might expect of a carcinoma originating from misplaced pancreatic tissue in the submucosa or between the muscle layers of the duodenum and spreading from this site of origin inward toward the lumen and outward into the surrounding retroperitoneal fat. It was concluded, therefore, that the carcinoma originated in the duodenum, not, however, from the duodenal mucosa but from aberrant pancreatic tissue embedded in its wall.

#### SUMMARY AND CONCLUSIONS

The clinical, roentgenologic and pathologic features of primary carcinoma of the infra-ampullary portion of the duodenum as described in the literature are briefly reviewed. An additional case is presented. This occurred in a 35 year old man who had a typical clinical history. The roentgenologic diagnosis of neoplasm of the infra-ampullary portion of the duodenum was made preoperatively. The tumor presented the usual gross features of primary carcinoma of the duodenum located in the infra-ampullary portion, while its microscopic appearance suggested an origin from pancreatic tissue. The occurrence of pancreatic rests in the duodenum and elsewhere is much more frequent than is generally suspected, and it is suggested that such rests of pancreatic tissue may give rise to benign or malignant tumors, as has been reported in several instances. From the gross and microscopic appearance of the duodenal tumor in the case here reported, the conclusion was drawn that it was a carcinoma arising in aberrant pancreatic tissue in the infra-ampullary portion of the duodenum.



# THERAPEUTIC TRENDS AND OPERATIVE MORTALITY IN CASES OF OBSTRUCTIVE JAUNDICE

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The preoperative and postoperative management of patients with obstructive jaundice has evolved from a series of therapeutic contributions, each of which was in particular vogue for a period. The integral analysis of these methods is instructive, for it indicates the present trend, and forms a sounder basis not only for a modern therapeutic regimen but for further clinical and laboratory investigation. The factors that govern mortality in patients with obstructive jaundice and the philosophy of treatment that is soundest today are known to all. After synthetic vitamin K (menadione) and various related substances had been used parenterally for over one year with excellent results in the control of postoperative bleeding, the impression was obtained that at last the problem of the jaundiced patient undergoing surgical treatment, was under control.<sup>1</sup> This impression was not entirely correct. Indeed, mortality reports from other clinics often indicated no better, and perhaps poorer, results than in the era before the use of vitamin K. It is clear now that although vitamin K has reduced the incidence of postoperative bleeding the hard learned lessons of the period prior to the introduction of vitamin K appear to have been too often ignored in practice. By now it seems just as unreasonable to rely entirely on vitamin K in preparing jaundiced patients for operation as to rely on insulin alone in the treatment of diabetic acidosis. After its spectacular advent in this hospital it was learned that vitamin K is not the sine qua non, but an adjunct in treatment, along with diet, transfusions of blood and plasma and other measures. To emphasize this thesis, I wish to present the experience at this clinic for the last three years.

It is worth while to reconsider, as a background to this report, the therapy prior to the introduction of vitamin K. In disease of the gallbladder with obstruction of the common duct, the following mortalities have been reported: Mayo<sup>2</sup> (1920), over 15 per cent; Walters<sup>3</sup> (1923), 10 per cent; de Takáts<sup>4</sup> (1924), 30 per cent; Ravdin, Rhoads, Frazier and Ulin<sup>5</sup> (1938), 14 per cent, and Illingworth<sup>6</sup> (1939), 11 per cent; Hunt<sup>7</sup> reported an operative mortality of 31 per cent among patients with carcinoma of the pancreas. The recent reports have made much of the

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1. Stewart, J. D.: Clinical and Experimental Evidence on the Nutritional Requirements in Obstructive Jaundice, *New England J. Med.* **223**:1059, 1940.

2. Mayo, C. H.: Jaundice: Surgical Significance, *Surg., Gynec. & Obst.* **30**:545, 1920.

3. Walters, W.: Physiologic Considerations in the Treatment of Obstructive Jaundice, *J. A. M. A.* **87**:2153 (Dec. 25) 1926.

4. de Takáts, G.: Some Problems of Jaundice and Their Significance in Surgery, *Ann. Surg.* **79**:662, 1924.

5. Ravdin, I. S.; Rhoads, J.; Frazier, W., and Ulin, A. W.: The Effect of Recent Advances in Biliary Physiology on the Mortality Following Operation for Common Duct Obstruction, *Surgery* **3**:805, 1938.

6. Illingworth, C. F. W.: Hemorrhage in Jaundice, *Lancet* **1**:1031, 1939.

7. Hunt, V. C.: Surgical Management of Carcinoma of the Ampulla of Vater and of the Periampullary Portion of the Duodenum, *Ann. Surg.* **114**:570, 1941.

incidence of bleeding and the prothrombin time; relatively infrequent is a full report on operative mortality. At the outset, therefore, it would be well to define the bases for my analysis. By jaundice I mean primarily obstructive jaundice. I am interested in the patients who are clinically jaundiced at the time of operation. The death of any patient who died by the thirtieth postoperative day, regardless of cause, or who died as a direct result of the operative procedure regardless of time, is considered an operative death. One further qualification seems obvious. The seriousness of this particular illness will vary in different localities.<sup>8</sup> The more seriously ill patients, clinically almost moribund and with far advanced pathologic changes, will be found in a charity institution like the Cincinnati General Hospital. The percentage of malignant lesions in the total number of cases and the type of operation must also be kept in mind.

Postoperative hemorrhage has since 1891 been recognized as an important cause of operative death of patients with obstructive jaundice.<sup>9</sup> In the past two decades, trends of therapy have been guided by investigations into the clotting defect as well as by studies of hepatic pathology and physiology. In 1926 Walters<sup>3</sup> emphasized the fact that with obstruction of the biliary tract there is impairment of hepatic function from the very beginning. Even with simple disease of the gallbladder, extensive hepatitis may exist,<sup>10</sup> and in such circumstances quantitative studies of the bile often reveal hepatic disturbance before obstruction of the common duct occurs. The pathologic changes in the liver produced by obstruction in the biliary tree were demonstrated by Counsellor and McIndoe.<sup>11</sup> They described the pathogenesis of so-called hydrohepatosis. MacCallum<sup>12</sup> emphasized the factors of infection and back pressure. Finally there was described the picture of fatty accumulation in the hepatic cell in the presence of obstruction of the liver.<sup>13</sup>

The question of hepatic lipid is coming more and more to the fore as a pathophysiologic problem. The first attempt to solve it clinically was with administration of carbohydrate. This idea of carbohydrate therapy, glycogenesis and the significance of hepatic glycogen in relation to injury of the liver arose from the concepts promulgated by Rosenfeld in 1900.<sup>14</sup> He indicated the reciprocal relationship between hepatic glycogen and hepatic lipid. In this country in 1915, Opie and Alford<sup>15</sup> first reported experiments on animals and worked out protocols in regard to study of the composition of the liver in relation to diet and toxins. They found that a high carbohydrate diet conditioned the livers of experimental animals to withstand exposure to chloroform, whereas a high fat diet induced a singular susceptibility to such exposure. In 1926 Walters<sup>3</sup> stated that at the Mayo Clinic patients with obstructive jaundice were given a high carbohydrate diet, supplemented with

8. Ravdin, I. S.: *Surgical Problems of Jaundice*, J. M. Soc. New Jersey **23**:341, 1926.

9. (a) Ivy, A. C.; Shapiro, P. F., and Melnick, P.: *Bleeding Tendency in Jaundice*, Surg., Gynec. & Obst. **60**:781, 1935. (b) Walters, W.: *Treatment of Obstructive Jaundice and Its Complications*, California & West. Med. **29**:77, 1928.

10. (a) Ravdin, I. S.: *Surgical Diseases of the Extrahepatic Bile Ducts*, New England J. Med. **220**:326, 1939. (b) Boyce, F.: *The Role of the Liver in Surgery*, Springfield, Ill., Charles C Thomas, Publisher, 1941, p. 37.

11. Counsellor, V. S., and McIndoe, A. H.: *Dilatation of Bile Ducts*, Surg., Gynec. & Obst. **43**:729, 1926.

12. MacCallum, W. G.: *Obstructive Biliary Cirrhosis*, in *Text Book of Pathology*, ed. 6. Philadelphia, W. B. Saunders Company, 1936, p. 315.

13. Schnedorf, J. G., and Orr, T. G.: *Fifty-Two Proven Cases of Carcinoma of the Pancreas and Ampulla of Vater, with Special Reference to Fatty Infiltration of the Liver*, Ann. Surg. **114**:603, 1941. Ravdin, Rhoads, Frazier and Ulin.<sup>5</sup>

14. Rosenfeld, G.: *Fettbildung*, Ergebn. d. Physiol. **2**:50, 1903.

15. Opie, E. L., and Alford, L. B.: *The Influence of Diet on Hepatic Necrosis and Toxicity of Chloroform*, J. A. M. A. **62**:895 (March 21) 1914.

dextrose when necessary. Ravdin, Riegel and Morrison<sup>16</sup> reported that clinically dextrose exerts a protective action if the liver is not injured beyond a certain degree of repair. In 1932 Cowan and Wright<sup>17</sup> reported that the damaged liver rapidly takes up intravenously administered dextrose. Recently Ravdin<sup>18</sup> and later Stewart<sup>1</sup> well reviewed the problem of metabolism associated with the pathology and physiology of the liver.

As for the postoperative hemorrhage of jaundiced patients, it is no longer believed that a quantitative deficiency in the blood calcium is responsible.<sup>19</sup> In 1930, calcium was still in vogue as the one specific single prophylactic agent used in preparing jaundiced patients for operation.<sup>5</sup> The work of Cowan and Wright,<sup>17</sup> of Ravdin, Riegel and Morrison<sup>16</sup> and of Cantarow, Dodek and Gordon<sup>20</sup> seemed to indicate that there is some relation between dextrose metabolism, hepatic function and calcium. All of these investigators suggested that obstructive jaundice is associated with a disturbance in some phase of that relationship. As late as 1938, Walters<sup>21</sup> still believed that calcium is beneficial. Apparently it is most indicated when hypoproteinemia is present.

The history of the significant therapeutic periods, as outlined by Ravdin, Rhoads Frazier and Ulin,<sup>5</sup> reveals that prior to 1929 preoperative preparation was little stressed. Great reliance was placed on the use of calcium and postoperative blood transfusions were given only occasionally. By 1929 the clinicians closed the gap between practice and experimental evidence indicating the importance of hepatic function in cases of obstructive jaundice. I need only mention the advances made in appreciation and utilization of the principles of fluid and electrolyte balance. Transfusions were still given only occasionally and always postoperatively. Stress was placed on high carbohydrate diets supplemented with intravenous administration of dextrose. From 1933 to 1937 blood transfusion preoperatively as well as postoperatively became established, not only as the best means of combating the hemorrhagic diathesis but as an excellent general supportive measure. Furthermore, in 1935 Snell<sup>22</sup> reported that of 40 patients who died of chronic parenchymatous disease of the liver 80 per cent had edema of the pulmonary bases, terminal bronchopneumonia or hydrothorax. However, the pulmonary lesions were supposed to be terminal pneumonia, except that the edema of the alveolar walls was considered of possible significance. These observations Snell correlated with the discovery of anoxic anoxemia in patients with obstructive jaundice. For this reason, Judd, Snell and Hoerner<sup>23</sup> subsequently emphasized the importance of

16. Ravdin, I. S.; Riegel, C., and Morrison, J. L.: Coagulation of Blood: Comparative Value of Calcium and Glucose in Decreasing Clotting Time, *Ann. Surg.* **91**:801, 1930.

17. Cowan, D. W., and Wright, H. N.: The Interrelationship Between Blood Sugar, Blood Calcium and Blood Coagulability, *Am. J. Physiol.* **100**:40, 1932.

18. Ravdin, I. S.: (a) The Protection of the Liver from Injury, *Surgery* **8**:204, 1940; (b) Progress in the Pre-Operative and Post-Operative Care of Patients with Lesions of the Biliary Tract, *Bull. New York Acad. Med.* **17**:500, 1941.

19. Gunther, L., and Greenberg, D. M.: The Diffusible Calcium and Proteins of Blood Serum in Jaundice, *Arch. Int. Med.* **45**:983 (June) 1930. Linton, R. R.: Relation of Calcium to the Hemorrhagic Tendency in Obstructive Jaundice, *Ann. Surg.* **93**:707, 1931. Wangenstein, O. H.: Hemorrhagic Diathesis of Obstructive Jaundice and Its Treatment, *ibid.* **88**:845, 1928. Ravdin, Riegel and Morrison.<sup>16</sup>

20. Cantarow, A.; Dodek, S. M., and Gordon, B.: Calcium Studies in Jaundice, *Arch. Int. Med.* **40**:129 (Aug.) 1927.

21. Walters, W., in discussion on Butt, Snell and Osterberg.<sup>25</sup>

22. Snell, A. M.: Chronic Liver Disease: Its Effect on the Blood, *Ann. Int. Med.* **9**:690, 1935.

23. Judd, E. S.; Snell, A. M., and Hoerner, M. T.: Transfusion for Jaundiced Patients. *J. A. M. A.* **105**:1653 (Nov. 23) 1935.

administration of oxygen and transfusion of blood as measures to increase the arterial saturation of oxygen in persons with obstructive jaundice.

The more important therapeutic measures that were evolved before the introduction of vitamin K<sup>24</sup> may be summarized as giving of calcium, use of a high carbohydrate diet, oral and intravenous administration of dextrose, attention to fluid intake and electrolyte balance, transfusion of blood, administration of oxygen, better choice and use of anesthetics, preoperative observation over longer periods of time, waiting for a decrease in the level of bilirubin in the blood, evaluation of any existing complications, use of bile preparations, and finally gradual postoperative decompression of the biliary system.<sup>5</sup> Although the incidence of bleeding remained the same, mortality due to hemorrhage and operative mortality were halved. Ravdin, Rhoads, Frazier and Ulin<sup>5</sup> in 1938 reported a mortality of 2 per cent due to hemorrhage and a total operative mortality of 9 per cent. Judd, Snell and Hoerner<sup>23</sup> reported an operative mortality of 4 per cent in 1935. The most evident improvement occurred subsequent to 1929, coincident with the increased use of dextrose and high carbohydrate diets and parenteral administration of fluids. By 1933, when the use of preoperative transfusion had become established, the best mortality figures for the decade were in the making.

Thus it may be seen that by 1937, although the fundamental fault in the coagulative mechanism in the blood of jaundiced patients was not generally understood, a therapeutic regimen had been elaborated that gave relatively good results. In commenting on the report of Butt, Snell and Osterberg<sup>25</sup> on the use of vitamin K at the Mayo Clinic, Walters<sup>24</sup> pointed out that mortality due to hemorrhage had been low at the clinic even before the use of vitamin K. His figure of 5 per cent for 400 operations performed during 1936-1937 suggests an apparently rosier picture than exists at most clinics. But that is a report not for total operative mortality but for mortality due to hemorrhage. At any rate, the system of therapy previously described had reduced the mortality but not the incidence of bleeding. It appeared that the discovery of the cause of bleeding and the rectification of this physiologic defect would be the final answer to the problem of operative mortality.

The tremendous interest and effort of investigators along this line were soon to bear results.<sup>26</sup> It was the correlation of disconnected observations spread over a decade that eventually gave the solution and culminated in the use of vitamin K in the hemorrhagic diathesis of patients with obstructive jaundice. By 1939 the isolation of concentrated, supposedly pure vitamin K had been achieved, to be followed by the synthesis of substances with vitamin K activity and the initiation of parenteral therapy.<sup>27</sup> As for the administration of vitamin K, Butt, Snell and Osterberg<sup>25</sup> in 1938 urged the preoperative classification of jaundiced patients as to hazard. With such patients a preoperative determination of prothrombin time is probably as important as any test of hepatic function. Even when prothrombin time was normal Butt, Snell and Osterberg insisted on prophylactic therapy with

24. Ravdin, I. S., and Johnston, C. G.: The Hemorrhagic Tendency of Obstructive Jaundice, *Am. J. M. Sc.* **193**:278, 1937. Ravdin.<sup>5</sup>

25. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: Further Observations: Use of Vitamin K in Hemorrhagic Diathesis in Cases of Jaundice, *Proc. Staff Meet., Mayo Clin.* **13**:753, 1938.

26. Dam, H.: Fat-Soluble Vitamins: Vitamin K, in Luck, J. M., and Smith, J. H. C.: *Annual Review of Biochemistry*, Stanford University, Calif., Annual Reviews, Inc., 1940, vol. 9, p. 362. Quick, A. J.: Prothrombin in Hemophilia and in Obstructive Jaundice, *J. Biol. Chem.* **109**:lxxxiii, 1935. Opie and Alford.<sup>13</sup>

27. (a) Norcross, J. W., and McFarland, M. D.: Intravenous Use of 2-Methyl-1,4-Naphthoquinone in Hypoprothrombinemia, *J. A. M. A.* **115**:2156 (Dec. 21) 1940. (b) Stewart, J. D.: Oral and Parenteral Use of Synthetic Vitamin K Active Substances in Hypoprothrombinemia, *Surgery* **9**:212, 1941.

vitamin K. Postoperatively, they followed their patients with prothrombin determinations for eight days. Ordinarily, vitamin K could well be given orally. But when values of prothrombin approach the critical level or there is actual bleeding, they as well as others (Norcross and McFarland,<sup>28a</sup> Stewart,<sup>28</sup> Stewart and Rourke,<sup>29</sup> Ravdin<sup>18b</sup> and Collier and Farris<sup>30</sup>) have advised parenteral administration. The majority of the clinicians have found intravenous administration the most effective and rapid method of lowering the prothrombin time to normal. Today it is generally agreed that failure to respond to parenterally administered vitamin K can be considered as an ominous prognostic sign. Can the prothrombin time itself and the response to vitamin K therapy be used as a test of hepatic function? Ziffren, Owen, Warner and Peterson<sup>31</sup> recently discussed this point and, apparently using the finer laboratory method of Warner and his associates,<sup>32</sup> showed that variations in prothrombin time can be readily disclosed and may be a reliable indication of hepatic function, at least as far as prothrombin is concerned.

The reports on the use of vitamin K indicate rather uniform success in reducing the incidence of postoperative hemorrhage. Figures for operative mortality are incomplete, but there appears to be no remarkable improvement. Butt, Snell and Osterberg<sup>25</sup> (1938) reported 3.1 per cent for 64 cases; Rhoads<sup>23</sup> (1939), 8.1 per cent for 12 cases, and Illingworth<sup>6</sup> (1939), 8.5 per cent for 14 cases. Stewart<sup>28</sup> (1939) gave no mortality figure for 27 cases but stated that 7 patients had massive postoperative bleeding. Stewart<sup>27b</sup> (1941) gave 20 per cent as the operative mortality for 20 cases. All these reports are for cases in which vitamin K was given orally. In 1941, after using subcutaneous injections of a synthetic substance with vitamin K activity (the sodium bisulfite derivative of methyl naphthoquinone) in the treatment of 14 patients, Stewart<sup>27b</sup> reported an operative mortality of 7 per cent. Norcross and McFarland<sup>27a</sup> (1940) who used intravenous injections of synthetic vitamin K (menadione) did not report mortality, but from their table it appears that for the 15 cases in which operation was done there was an operative mortality of 20 per cent. Hunt<sup>7</sup> (1941) reported a 21 per cent mortality for cases of carcinoma of the pancreas. In 1941 operative mortality for cases of obstructive jaundice was 19 per cent in the Cincinnati General Hospital.

Although in 1939 and 1940 the opinion prevailed that the case in which hypoprothrombinemia due to obstructive jaundice would not respond to K was rare, it appears now that this is not true. Every author has a failure or two to report, though the total number of such failures in any series is usually small. To some extent it appears that perhaps too much reliance has been placed on vitamin K. As Walters<sup>21</sup> pointed out, one must not forget the lessons learned before the introduction of vitamin K therapy. Obviously, its intrinsic value has been more than that of a weak prosthetic to a defective prothrombin mechanism. However, the use

28. Stewart, J. D.: Prothrombin Deficiency and the Effects of Vitamin K in Obstructive Jaundice and Biliary Fistulae, *Ann. Surg.* **109**:588, 1939.

29. Stewart, J. D., and Rourke, G. M.: Control of Prothrombin Deficiency in Obstructive Jaundice by Use of Vitamin K, *J. A. M. A.* **113**:2223 (Dec. 16) 1939.

30. Collier, F. A., and Farris, J. M.: The Management of the Jaundiced Patient with Special Reference to Vitamin K, *Surg., Gynec. & Obst.* **73**:21, 1941.

31. Ziffren, S. E.; Owen, C. A.; Warner, E. D., and Peterson, F. R.: Hypoprothrombinemia and Liver Function, *Surg., Gynec. & Obst.* **74**:463, 1942.

32. Smith, H. P.; Warner, E. D., and Brinkhous, K. M.: Prothrombin Deficiency and Bleeding Tendency in Liver Injury, *J. Exper. Med.* **66**:801, 1937. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study of Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, *Am. J. Physiol.* **114**:667, 1936.

33. Rhoads, J. E.: The Relation of Vitamin K to Hemorrhagic Tendency in Obstructive Jaundice, with a Report on Cerophyl as a Source of Vitamin K, *Surgery* **5**:794, 1939.

of vitamin K certainly does not obviate the use of blood.<sup>34</sup> Also, as was pointed out by Butt, Snell and Keys,<sup>35</sup> in cases of obstructive jaundice with damage to the liver the total protein in the blood may well be within normal limits, but because of a lowered albumin content and reversal of the albumin-globulin ratio, the colloid osmotic pressure may be low, so that the indication for plasma may be more urgent than it appears to be. Finally, even when vitamin K is administered parenterally there is indication for the use of bile for reasons other than that it promotes absorption of vitamin K from the intestinal tract.

Counsellor and McIndoe<sup>11</sup> doubted that the reserve of the liver would be overcome by even the most advanced obstructive hepatic syndrome. But to any one who has followed patients with obstructive jaundice and studied their livers at autopsy, this conclusion seems unreasonable. The unexpected appearance of

TABLE 1.—*Patients with Obstructive Jaundice Operated on*

	Patients	Deaths	Operative Mortality, per Cent
1939.....	14	5	36
1940.....	12	4	33
1941.....	16	3	19
Total.....	42	12	29

TABLE 2.—*Obstructive Jaundice Due to Carcinoma of the Head of the Pancreas*

	Patients	Deaths	Operative Mortality, per Cent
1939.....	8	4	50
1940.....	4	2	50
1941.....	8	1	13
Total.....	20	7	35

TABLE 3.—*Patients with Obstruction of the Common Duct Not Due to a Malignant Growth*

	Patients	Deaths	Operative Mortality, per Cent
1939.....	6	1	17
1940.....	8	2	25
1941.....	8	2	25
Total.....	22	5	23

hemorrhage postoperatively, the conviction that many elderly patients and many patients in whom the obstructive syndrome is superimposed on such a pathologic condition as cirrhosis or malignant metastases receive a knockout blow from operative trauma and anesthesia, and now the lack of response to vitamin K of about 10 per cent of all these patients with obstructive jaundice seem conclusive evidence that the liver is far from inexhaustible in its performance and is not invulnerable to trauma, toxemia and anoxia.

In the light of the foregoing discussion, the record of the 42 patients with jaundice operated on in this clinic in the past three years can now be examined. Forty-eight per cent of the obstructions of the common duct were due to malignant tumors. I discarded many cases of stone in the common duct because of inadequate

34. Karabin, J. E.; Udesky, H., and Seed, L.: Effect of Stored Citrated Blood Transfusion upon Patients with Hypoprothrombinemia, Surg., Gynec. & Obst. **73**:10, 1941.

35. Butt, H. R.; Snell, A. M., and Keys, A.: Plasma Protein in Hepatic Disease: Study of Colloid Osmotic Pressure of Blood Serum and of Ascitic Fluid in Various Diseases of the Liver, Arch. Int. Med. **63**:143 (Jan.) 1939.

data concerning jaundice. None of the cases from the private services was considered. It is not absolutely important to compare mortality figures with those from other hospitals; it is important, however, to watch the mortality in any given clinic from year to year. According to the standards of selection that have been set, it is now possible to scrutinize the results of therapy for the type of patient treated at the Cincinnati General Hospital (tables 1, 2 and 3).

Tables 4 and 5 show the types of operation that were done.

It will be seen that in 65 per cent of the cases of malignant disease a major palliative operation was performed. The patients who had had only an exploratory laparotomy were of course the sickest, and no special effort was made postoperatively to prolong their life.

The figures show that although in 1941 about 50 per cent of the patients had malignant growths and about the same type of major surgical procedure was being done on all, the operative mortality was distinctly lower. In cases of malignant tumor a reduction from 50 per cent to 13 per cent was achieved. As

TABLE 4.—Operations Performed on Twenty Patients with Obstruction of the Common Duct Due to a Malignant Tumor

	Patients	Died	Mortality, per Cent
Exploratory laparotomy and biopsy.....	7	3	43
Palliative (cholecystgastrostomy, etc.).....	6	2	33
Whipple operation (3 patients had first stage only).....	7	2	29
Total.....	20	6	35

TABLE 5.—Operations Performed on Twenty-Two Patients with Obstruction of the Common Duct Not Due to a Malignant Growth

	Patients	Died	Mortality, per Cent
Cholecystectomy and exploration and drainage of common duct.....	17	3	18
Exploration and drainage of common duct.....	2	0	0
Cholecystgastrostomy.....	2	2	100
Choledochoduodenostomy.....	1	0	0
Total.....	22	5	23

far as age, debilitation, diabetes and pulmonary and nephritic complications are concerned the 1941 patients, if not sicker than usual, were the ordinary run. Consequently, there arise certain pointed questions concerning our preoperative and postoperative therapy. These questions and their answers had been considered in 1940 with apparent beneficial results.

How was vitamin K given, and what response was obtained? The response to oral and parenteral administration was satisfactory. In the majority of cases the degree of jaundice was measurable by an icteric index of from 40 to 100. In only 2 cases was the prothrombin time, on admission, within normal limits. However, there was a preoperative record of this test in only 30 cases. Response to vitamin K was indicated by a return of prothrombin time to normal. Quick's method of determining prothrombin time was used.

Thirteen per cent of the patients treated did not respond. Two of these patients definitely did not receive adequate oral doses of the vitamin or of bile salts. In 1941 such excellent response was obtained from intramuscular administration that vitamin K was given intravenously in few instances. In using vitamin K<sup>36</sup>

36. The preparation used was klotogen (Abbott Laboratories). Each capsule contains 1,000 units of vitamin K as measured by the modified Almquist method.

orally our best results were obtained with capsules containing a concentrate of the vitamin in peanut oil and bile salts. Three to six of the capsules were given per day, and 2 Gm. of bile salts. The following is an example of reductions in prothrombin time (Quick) after two to three days of oral administration of vitamin K; patient G. K., twenty-five seconds to fourteen seconds; patient C. M. nineteen seconds to twelve seconds; patient G. L. seventy-six seconds to fifteen seconds.

In 1940 there was no postoperative hemorrhage. Vitamin K was being given more correctly, i. e., in larger doses of better preparations; blood transfusions were again being given preoperatively. At this time it was realized that, although vitamin K was being used successfully, operative mortality had not improved. Some of the more significant errors in our preoperative handling are listed as follows:

1. Too much emphasis was placed on tests of prothrombin time and of response to vitamin K as opposed to other tests of hepatic function, and clinical impressions were not sufficiently considered.

2. Vitamin K was prescribed in a haphazard fashion, with no plan for the specific needs of the patient. One patient who did not respond to intramuscular injections did not receive vitamin K intravenously.

TABLE 6.—*Response to Administration of Vitamin K*

Year	Patients	Oral	Intra-muscular	Intra-venous	No Response	Postoperative Bleeding
1939.....	10	10	0	0	2	4
1940.....	9	6	2	1	2	0
1941.....	11	0	9	2	1	1
Total.....	30	..	..	..	5	

3. Such forms of supportive therapy as blood transfusion and administration of bile and of oxygen, which used to be mainstays, were amazingly neglected.

4. The preoperative stay in the hospital was unusually short. Too often the patient was taken from the medical wards to the operating room. One normal value for prothrombin time following good response to vitamin K was considered to be sufficient evidence that the patient was ready for operation.

5. Postoperatively, the patient was not followed carefully enough, with determinations of prothrombin time.

6. Study of high carbohydrate, high protein and low fat diets and diets designed for the person with disease of the gallbladder revealed that those prescribed in the Cincinnati General Hospital were hardly suitable for the jaundiced patient. Too often they were high in caloric value and nothing more. The interns sent a routine requisition to the dietary department, where it was filled without an understanding of the individual problem. For instance, the most popular diet, called high carbohydrate, high protein, furnished 3,800 calories and consisted of 38 per cent carbohydrate, 42 per cent fat and 20 per cent protein, a far cry from the diet recommended by Ravdin.

7. Vitamin K seemed to have displaced other vitamins, such as vitamin C and the members of the B complex, from the order sheets.

8. Finally, no one person was interested in critical scrutiny of all the jaundiced patients, both as to administration of a therapeutic plan and study of the results.

In 1941, by rehabilitating all the measures proved effective before the introduction of vitamin K and by establishing a plan of vitamin K therapy according to the recommendations of Snell, we did far better. Even then, because the plan



was not rigidly adhered to, one patient who was not followed carefully had postoperative bleeding and subsequently died. In 1941, the average preoperative period in the surgical ward was seven days. My associates and I, made out the diets, to the last detail, in cooperation with the dietitians. We educated them to our problem and as far as necessary individualized the diets to meet the obvious practical problems. Thus, in 1940 the problem of hemorrhage was solved by the proper use of vitamin K, as it was in all other clinics. But not until now have I felt that the sum of our treatment made an intelligent answer to the problem of operative mortality in the jaundiced patient.

Could response to vitamin K as measured by the Quick test be used as a test of hepatic function? No response or a poor response is of gloomy prognostic significance. In 4 of the 5 patients who did not respond, hemorrhage was the major clinical cause of death. Two of our patients, H. H. and E. F., responded well to oral administration of vitamin K. At autopsy, both showed extensive damage to the liver. Clinically, the death of H. H. was due to hepatic failure. On the other hand, G. W., a patient operated on this year (and not included in the series), showed no response to intravenously administered vitamin K. Her progressively downhill course forced a decision; she was operated on and made an uneventful recovery with no evidence of postoperative bleeding. I can now recall the isolated cases reported by Illingworth, Butt and others, in which very low levels of prothrombin were not accompanied by postoperative hemorrhage. Coller and Farris<sup>30</sup> concluded that patients with severe hepatic damage that do not respond to vitamin K are rare. Ziffren's<sup>31</sup> report indicated some correlation between results of prothrombin tests, hepatic function and prognosis. However, the literature and my experience lead to equivocal conclusions. Again, all I can say is that prothrombin and tests for prothrombin as known today are not by any means the whole story in cases of obstructive jaundice.

The failure of vitamin K wholly to solve the problem of operative mortality once more focused attention on hepatic pathology and physiology. Recently Schnedorf and Orr<sup>18</sup> described extensive fatty changes seen in the liver in many patients with carcinoma of the head of the pancreas; they advised the clinical trial of certain lipotropic substances to correct the apparent fault in hepatic metabolism. In our cases we found the pathologic picture more complicated. Complete postmortem examinations were carried out on 8 of 12 patients who died. From another patient a specimen of the liver was obtained for biopsy. Examination of the structure and composition of the liver revealed that we were dealing mainly with fatty changes, necrosis, infection, sclerosis, degenerative changes in the hepatic cells themselves and malignant metastases. Of the 8 patients on whom autopsy was done, 100 per cent showed unquestioned pathologic changes in the lungs; 4 showed pathologic changes in the pancreas. Whereas clinically only 1 death was ascribed to hepatic failure, pathologically the liver was chiefly incriminated in 6 cases. Because of some toxicity, jaundice and postmortem changes significance cannot be attached to the pathologic changes observed in the pancreas.

In 1929 Ravdin and his co-workers<sup>37</sup> reported data derived from experiments on dogs in support of a newer concept of hepatic glycogen and lipids. They showed experimentally that a high protein as well as a high carbohydrate diet gives the best protection to the liver. Consequently, they have advocated the use of similar diets in the preparation of jaundiced patients for operation. Ravdin<sup>18</sup> advised an intake of at least 3,000 calories divided as follows: protein, 20 to 25 per cent; carbohydrate, 75 to 80 per cent; fat, less than 5 per cent. The use of interval

37. Ravdin, I. S.: Some Aspects of Carbohydrate Metabolism in Hepatic Disease, *J. A. M. A.* 93:1193 (Oct. 19) 1929.

feedings, the preparation of individual diets (as for a diabetic) and the administration of crystalline vitamin B<sub>1</sub> are stressed. Doubt is cast on the intravenous use of dextrose, at least as a sole preoperative measure. Still Cowan and Wright<sup>37</sup> and in 1939 Soskin and Hyman<sup>38</sup> stressed the value of intravenous administration of dextrose in providing a strong immediate stimulus for glycogenesis. It also forms a means of providing carbohydrates for patients who are desperately sick and unable to take an adequate diet.

At this point, it is important to distinguish between damage to the liver and degeneration of the liver, between the sequelae of a single trauma to a healthy dog's liver and those of a persistent noxious process in a human liver, a process which itself may be superimposed on preexisting pathologic changes and have added to it finally the trauma of anesthesia and operation. How well will desperately sick jaundiced patients handle an excessive intake of protein? What proteins and what amino acids are best handled? Are any actually injurious? The lipotropic effect of certain sulfamino acids has been described by investigators.<sup>39</sup> Recently, however, cystine has been incriminated as a possible hepatotoxic substance.

In 1939 Dragstedt and his associates<sup>40</sup> advanced the theory of a pancreatic lipotropic hormone called lipocaic, a fat-free pancreatic extract, small doses of which are effective in curing the fatty liver of pancreatectomized dogs. Although some amazing clinical results on fatty livers are reported in the literature on diabetes and on cardiac disease, lipocaic is still not recognized by the Council on Pharmacy and Chemistry.<sup>41</sup> It appears that the ordinary high protein diet for jaundiced patients will have to be modified in many respects.

#### SUMMARY

Trends in the treatment of jaundiced patients subjected to operation and their pathologic and physiologic basis are briefly and chronologically discussed.

Operative mortalities before and after the introduction of vitamin K are discussed. Vitamin K itself has not appeared to solve the problem of operative mortality in cases of obstructive jaundice. The reasons for failure are enumerated.

The results of 42 operations performed in the last three years are presented, with an analysis of the therapy, operative mortality and postmortem observations.

By the proper use of vitamin K, the problem of postoperative hemorrhage was solved; but it was only by the application of a complete therapeutic regimen that the operative mortality was significantly reduced.

Response to vitamin K as an index of hepatic function is discussed.

The pathologic changes in the liver are discussed. Some pathologic changes have been found in the pancreas, but their significance is doubtful.

38. Soskin, S., and Hyman, M.: Physiologic Basis of Intravenous Dextrose Therapy for Diseases of the Liver, *Arch. Int. Med.* **64**:1265 (Dec.) 1939.

39. Best, C. H.; Hershey, J. M., and Huntsman, M. E.: The Effect of Lecithin on Fat Deposition in the Liver of the Normal Rat, *J. Physiol.* **75**:56, 1932. Best, C. H.; Ferguson, G. C., and Hershey, J. M.: Choline and Liver Fat in Diabetic Dogs, *ibid.* **79**:94, 1933. Singal, S. A., and Eckstein, H. C.: The Lipotropic Action of Some Sulfur Containing Amino Acids and Related Substances, *J. Biol. Chem.* **140**:27, 1941.

40. Dragstedt, L. R.: The Present Status of Lipocaic, *J. A. M. A.* **114**:29 (Jan. 6) 1940. Dragstedt, L. R., and others, in discussion on Spellberg, M. A., and Keeton, R. W.: Influence of Various Substances on Fatty Livers Produced by Scorbuto-genic Diets, *ibid.* **114**:519 (Feb. 10) 1940. Dragstedt, L. R.; Vermeulen, C.; Goodpasture, W. C.; Donovan, P. B., and Geer, W. A.: Lipocaic and Fatty Infiltration of the Liver in Pancreatic Diabetes, *Arch. Int. Med.* **64**:1017 (Nov.) 1939.

41. The Present Status of Lipocaic, report of the Council on Pharmacy and Chemistry, *J. A. M. A.* **115**:1454 (Oct. 26) 1940.

# INFILTRATION OF BONE WITH SPONTANEOUS FRACTURE IN A CASE OF CHRONIC MYELOGENOUS LEUKEMIA

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The bone marrow in leukemia is the seat of a diffuse hyperplastic process extending throughout all marrow-containing bones. The spongy trabeculae are destroyed, and the cortex of the long bones becomes thin. On microscopic examination the lesions in bone appear to be due to pressure and growth, local or diffuse, within the bone rather than to loss of blood supply. In some instances there is a direct extension of the leukemic process through the cortex, the periosteum being lifted by the formation of small subperiosteal tumor masses. These masses may extend into the surrounding soft tissues.

Roentgenograms of the skeleton of patients with leukemia show a variable picture. The bones involved in order of frequency are the pelvis, the lumbar vertebrae, the neck of the femur, the head of the humerus and the skull, and less often the metacarpal bones, the ulna, the tibia and the fibula. In the lymphatic leukemias osteoclastic and osteosclerotic changes are observed. In the myeloid type both osteolytic and osteosclerotic lesions have been described, with diffuse or localized areas of rarefaction or sclerosis. In both types of leukemia periostitis and periosteal elevation may be seen.

Craver and Copeland<sup>1</sup> studied 169 cases of leukemia, 86 of lymphatic and 83 of myelogenous. In 7 per cent of the cases in the former group osseous involvement was seen on roentgenographic examination. In only 1 of the cases of myelogenous leukemia was osseous involvement found. No fractures were observed. In children the disease apparently involves the skeletal structures more frequently. Snelling and Brown<sup>2</sup> described 12 cases of lymphatic leukemia in patient under the age of 6 and found that in 8 there was rarefaction at the ends of the long bones and in 4 there were periosteal elevations. The following year Baty and Vogt<sup>3</sup> studied the roentgenograms of 60 children with leukemia and found that there was diminished density just proximal to the metaphyses of the long bone in 43 of them. In 2 there was periosteal elevation. The following year Baty and Forkner<sup>4</sup> reviewed case reports of osseous involvement up to 1938 and discussed the histopathologic picture. Since that date a paper has appeared on this subject by Mendl and Saxl,<sup>5</sup> who described 3 cases of leukemia in which there was roentgen evidence of involvement of bone.

From the Radiation Therapy Service, Kings County Hospital.  
1. Craver, L. F., and Copeland, M. M.: Changes of the Bones in the Leukemias, *Arch. Surg.* **30**:639 (April) 1935.

2. Snelling, C. E., and Brown, A.: Bone Changes in Leukaemia: Clinical and Roentgenological, *Arch. Dis. Childhood* **9**:315, 1934.  
3. Baty, J. M., and Vogt, E. C.: Bone Changes of Leukemia in Children, *Am. J. Roentgenol.* **34**:310, 1935.  
4. Forkner, C. E.: Leukemia and Allied Disorders, New York, The Macmillan Company, 1938, p. 108.  
5. Mendl, K., and Saxl, O.: Bone Changes in Leukemia, *Am. J. Roentgenol.* **44**:31, 1940.

In 1913 Pförringer<sup>6</sup> reported the first case of spontaneous fracture occurring in a patient suffering from lymphatic leukemia. A woman aged 50 sustained a fracture of one femur, followed a month later by fracture of the other femur while the patient was still confined to bed. At autopsy lymphatic leukemia was found. In 1931 Trusen<sup>7</sup> described the case of a child of 5 years who had severe anemia and leukopenia. The white cells numbered 2,800, of which 92 per cent were lymphocytes. The child was thought to have an acute aleukemic lymphatic leukemia. During the course of the illness the patient suffered a spontaneous fracture of the right femur. The child subsequently died, and at autopsy the typical changes of lymphatic leukemia were noted.

#### REPORT OF A CASE

E. L., a white woman aged 52, was first admitted to Kings County Hospital on Aug. 17, 1938 because of an enlarged mass in the abdomen, weakness, fever and backache. The past



Fig. 1.—Variations in the total number of leukocytes and dosage of irradiation. At P skeletal roentgenograms were normal; at T there was pain in the right thigh, but a roentgenogram revealed no abnormality; at X occurred a fracture of the right femur. In the lower portion of the figure are indicated the dates, amounts and sites of irradiation: K, to the kidneys; S, to the spleen; C, to the cervical region of the spine; D, to the dorsal region of the spine; L, to the lumbar region of the spine; F, to the right femur, and Q, to the right forearm.

medical history was entirely noncontributory. The present illness had begun two years previously. The patient had been admitted to another hospital, where the diagnosis of chronic myelogenous leukemia was made. She received roentgen therapy there, but the data are not available. On physical examination the most significant observations were limited to the

6. Pförringer, D.: Ein Fall von Leukämie mit tumorartigen zu Spontanfrakturen führenden Markwucherungen, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 20:405, 1913.

7. Trusen, M.: Spontanfraktur bei einem Kinde mit lymphatischer Leukämie, *Monatschr. f. Kinderh.* 50:45, 1931.

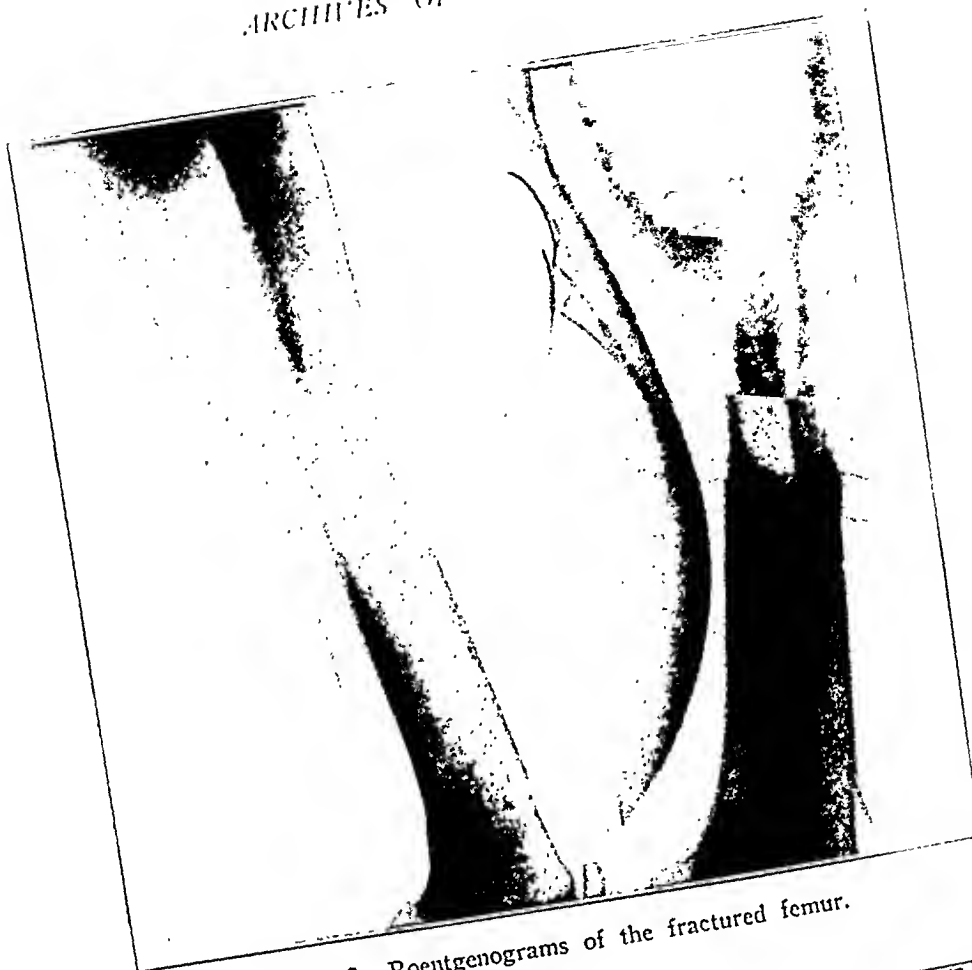


Fig. 2.—Roentgenograms of the fractured femur.

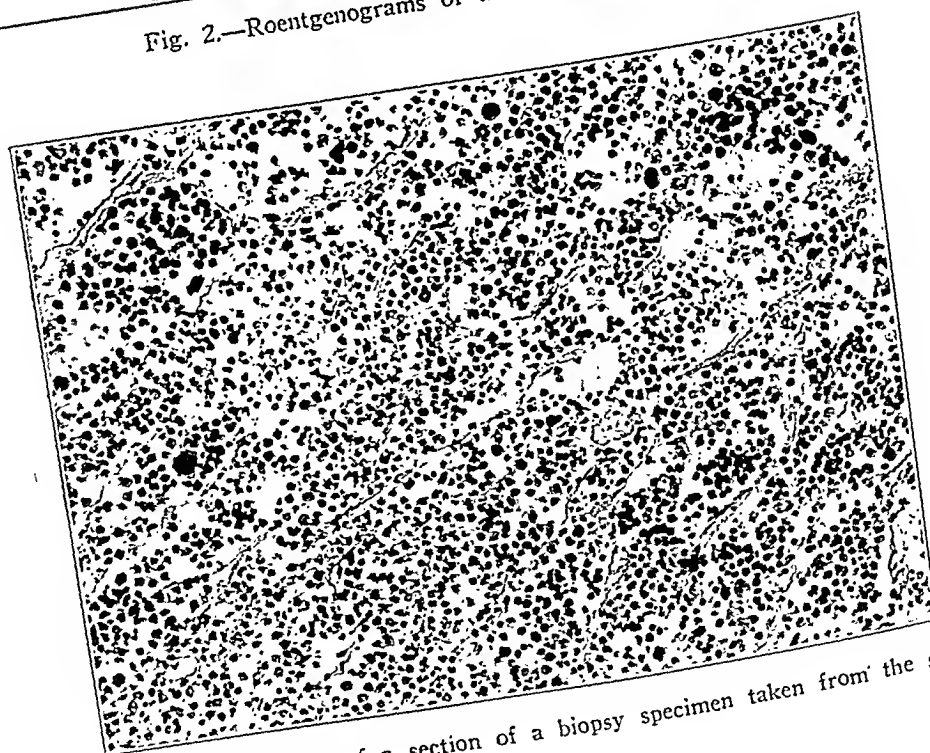


Fig. 3.—Photomicrograph of a section of a biopsy specimen taken from the site of the fracture.

abdomen. The liver was enlarged, extending 4 fingerbreadths below the costal margin; the spleen was below the umbilicus and extended to the midline. The patient appeared pale and apprehensive. No enlarged lymph nodes were felt. The blood count and all subsequent hematologic studies are presented in figure 1. Temperature, pulse rate and respiratory rate were 100.2 F., 82 and 22 respectively. The blood pressure was 108 systolic and 64 diastolic. The urea content of the blood was 38 mg. per hundred cubic centimeters, the sugar content 88 mg. and the calcium content 10.4 mg. Roentgenograms of the skeletal structures disclosed no involvement of bones. The Wassermann reaction of the blood was negative.

As shown in figure 1, the patient was treated by irradiation of the region of the kidneys, which produced a rapid fall in the number of leukocytes and improvement in her general condition. She was followed in the radiation therapy leukemia clinic. There was a gradual rise in the number of white cells, and three months later radiation to the spleen was given. A reduction of the number of white blood cells and clinical improvement were again produced. Two months later splenic irradiation was again instituted, the white cell count falling to 14,000. The patient's course followed this pattern until her admission to the hospital, on Oct. 23, 1939, three years after the onset of her illness. At this time she appeared acutely ill, and a tender, painful mass was noted on the anterior aspect of the right thigh. Ten days later, while in bed, the patient suffered a spontaneous fracture of the lower third of the right femur. Roentgenograms showed a fracture at the middle of the lower third of the femur with an area of destruction in the medullary portion of the shaft (fig. 2). The total number of white cells was then 105,000 per cubic millimeter of blood. Russell traction was applied to the injured limb. The patient's course was rapidly downhill, in spite of a gradual fall in the number of white cells. Anemia became more pronounced, and death occurred two months after the fracture. A biopsy specimen taken from the site of the fracture shortly before death showed an area of absorption of bone in which there was an infiltration of cells, mainly myeloblasts and myelocytes (fig. 3). The total duration of the illness was about three and one-half years.

#### SUMMARY

A case of spontaneous pathologic fracture of the femur in a patient with chronic myelogenous leukemia is presented. It emphasizes the need for repeated and complete skeletal examinations of patients with chronic leukemia. When such examinations have been carried out as a routine measure, several interesting and unexpected, as well as symptom-free, osseous lesions have been detected. When the universal distribution of the pathologic changes in the leukemic and lymphoblastomatous diseases is recognized, the occurrence of osseous lesions is not surprising. The infrequency with which they are found suggests the lack of routine and repeated roentgen examinations. The expense to the patient involved in a private hospital and the excess of routine in a municipal charity hospital are potent deterring factors.

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# ARTERIOSCLEROTIC GANGRENE

## A REPORT ON REFRIGERATION PRIOR TO AMPUTATION

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The staff of a large community hospital caring predominantly for charity patients is continually faced with the problem of managing cases of gangrene of the toes and feet due to arteriosclerosis. More often than not the patient does not apply for aid until the condition is well established and he is in an advanced toxic condition, or even moribund. The problem is usually complicated by the advanced age of the patient and the frequently associated heart disease, general toxicity and diabetes. It is now generally accepted<sup>1</sup> that amputation of the leg is necessary if the gangrene has extended proximal to the toes. The operation often constitutes a desperate emergency for patients with far advanced toxicity, and the results in the past have been persistently discouraging. As the technic of spinal anesthesia improved, more patients withstood operation and the problem became more hopeful, but to save the life of an extremely toxic patient with advanced gangrene requiring immediate operation still constituted a difficult problem. With the publication of the work of Allen and his associates<sup>2</sup> on the refrigeration of gangrenous limbs new hope was held out for many patients who previously would have been lost.

While investigating tissue metabolism and local asphyxia in 1938, Allen<sup>3</sup> showed that a narrow elastic tourniquet about a limb causes less local damage to the tissues than a wide one. Later he<sup>4</sup> added chilling of the tissue to occlusion of the blood supply by the tourniquet and found that the length of life of the tissues was remarkably extended. Brooks and Duncan<sup>5</sup> in 1940 proved the same point by experiment on rats, finding that gangrene always develops in a rat's tail subjected to pressure of 130 mm. of mercury for eighteen hours at room temperature, whereas at 1 C. (33.8 F.) it fails to undergo gangrenous changes even after ninety-six hours of the pressure.

### METHOD

For the maintenance of the cooling effect on these limbs we had a simple metal box made, long enough to hold the whole leg (figs. 1 and 2). The top is open, and a hole at one end permits entrance of the leg and thigh. A partition, which is

From the Peripheral Vascular Service, Baltimore City Hospitals.

1. McKittrick, L. S.: Diabetic Gangrene: Review of Nine Hundred and Seventy-Two Cases of Gangrene Associated with Diabetes Mellitus, Arch. Surg. 40:352-363 (Feb.) 1940.  
Macey, H. B., and Bickel, W. H.: Amputation of the Lower Extremities in Occlusive Arterial Diseases, Surg., Gynec. & Obst. 74:821-827 (April) 1942.

2. (a) Allen, F. M.: Surgical Considerations of Temperature in Ligated Limbs, Am. J. Surg. 45:459-464 (Sept.) 1939. (b) Crossman, L. W.; Ruggiero, W. F.; Hurley, V., and Allen, F. M.: Reduced Temperatures in Surgery: Amputations for Peripheral Vascular Disease, Arch. Surg. 44:139-156 (Jan.) 1942. (c) Allen F. M.: Experiments Concerning Ligation and Refrigeration in Relation to Local Intoxication and Infection, Surg., Gynec. & Obst. 68:1047-1051 (June) 1939.

3. Allen, F. M.: Tourniquet and Local Asphyxia, Am. J. Surg. 41:192-200 (Aug.) 1938.

4. Allen, F. M.: Resistance of Peripheral Tissues to Asphyxia at Various Temperatures, Surg., Gynec. & Obst. 67:746-751 (Dec.) 1938; footnote 2c.

5. Brooks, B., and Duncan, G. W.: Effects of Pressure of Tissues, Arch. Surg. 40:696-709 (April) 1940.

movable so as to come at the level of the knee, has a smaller hole through which the leg and foot pass. Drains near the bottom remove the water as the ice melts. A heavy rubber sheet is placed over the lower half of the bed. After insertion of the patient's leg the box is placed on the rubber sheet. The patient's buttocks are supported and raised by a rubber-covered pillow. The head of the bed is raised on

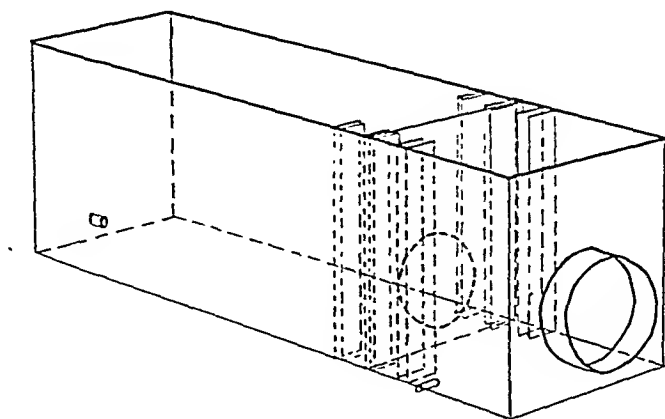


Fig. 1.—Metal box in which the limb is placed for chilling. The partition, shown in position for the average leg, is adjusted to come at the level of the knee by sliding it into the appropriate slots. Drains to which rubber tubing is attached remove water as the ice melts. All free edges of metal are rounded over wire.

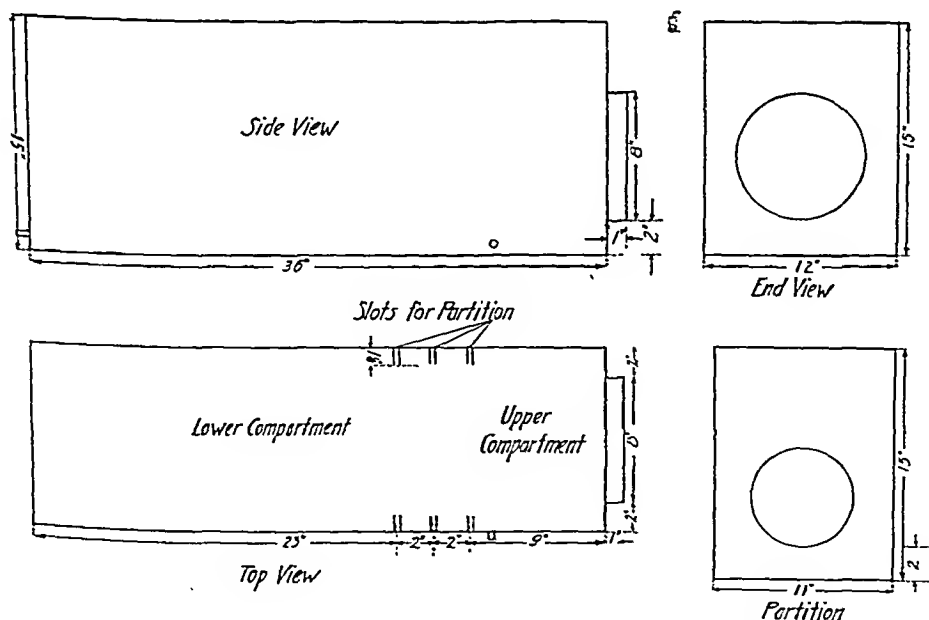


Fig. 2.—Same as figure 1, showing dimensions for construction.

6 inch (15 cm.) shock blocks, in order to keep the patient's leg well in the box and also to allow moisture which condenses on the outside of the box to drain off the foot of the bed. A small piece of rubber sheeting is cut, with a hole left which fits loosely around the patient's knee and yet blocks the hole in the partition of the box enough to prevent the ice from falling through to the upper compartment. A



second piece is fashioned for the upper part of the thigh, to block the hole in the end of the box. Finely chipped ice is now added to the lower compartment, covering the leg to the knee.

A half-hour later, when the leg is well numbed by the cold, a tourniquet of good quality gum tubing is placed about the leg at the level of the tibial tuberosity so that the ice extends 1 or 1½ inches (2.5 to 3.8 cm.) above the tourniquet. This tourniquet should be put on as tightly as possible, because the blood supply must be interrupted completely.

We have maintained this state for as long as ninety-six hours, although forty-eight hours is nearly always sufficient to bring the patient to the optimum condition for amputation. During this period general supportive measures are applied as indicated.

Six or eight hours prior to the time for operation the upper compartment is filled with ice, which should reach to the upper third of the thigh. A half-hour later a second tourniquet is tied tightly about the thigh 1 inch (2.5 cm.) below the line of chilling and yet definitely above the proposed operative field. This tourniquet must be tight enough to occlude the arterial supply unquestionably or anesthesia will not be complete. Amputation is performed between the two tourniquets, which are left in place, the anesthesia lasting for at least an hour and a half. After operation a thin dressing is applied to the stump which is then covered with bare ice bags for twenty-four hours. The patient does not have any meals deferred, preoperatively or postoperatively, and is permitted to sit up in a chair for an hour on the day of operation, after the procedure.

#### REPORT OF CASES

CASE 1.—The first patient who received the ice-tourniquet treatment, a woman 85 years of age, was brought to the accident room at about 5 p. m. on April 23, 1942, in an extremely debilitated condition. She had at first refused to come to the hospital, and it was only after she had been irrational for three days that relatives took matters into their own hands and brought her. She was extremely restless, her son stating that she had not slept for more than an hour at a time during the previous four months because of the severe pain in her left foot. She was considerably dehydrated, having been unable to swallow fluids for twenty-four hours. The temperature was 104 F., the pulse rate 100, the respiratory rate 24 and the blood pressure 160 mm. of mercury systolic and 90 diastolic. She was not diabetic, nor did she show signs of advanced heart disease. The distal two thirds of the left foot was gangrenous, with cellulitis and edema extending halfway to the knee. Altogether she belonged to the group of patients who inevitably die unless the leg is removed and who frequently die shortly after surgical intervention. On admission treatment by the ice-tourniquet technic was instituted. One hour later she dropped quietly off to sleep and slept soundly until morning. She received 2 liters of 5 per cent dextrose in physiologic solution of sodium chloride intravenously during the night. When she awoke, about 8 a. m., she presented the picture of an elderly woman who was alert, cooperative, able to eat her breakfast by herself and in complete control of her faculties. The temperature had fallen 5 degrees during the night, and it remained normal, the highest rise being to 99 F. on the third day. The pulse rate was 80 and the respiratory rate 20. She was cheerful and extremely relieved that the pain of her foot had at last stopped. When the question of amputation arose, she flatly refused, and it was only after it had been explained that the severe pain would return if the foot were removed from the ice that she consented. From this time she became mentally depressed, stating that she wished to die.

Forty hours after her admission to the hospital the level of the chipped ice was raised to the junction of the middle and the upper third of the thigh. A second tourniquet was tied tightly at the midthigh a half hour later. After six hours she was taken to the operating room where, with the two tourniquets still in place, a supracondylar amputation was performed. No sedative nor further anesthetic was used or needed. The blood pressure at the start of operation was 170 mm. of mercury systolic and 100 diastolic, and during the operation it rose smoothly to 195 systolic and 100 diastolic. The skin was closed tightly, without drainage, after the upper tourniquet had been removed. A light dressing was applied, and

the stump was surrounded by ice bags for the next twenty-four hours. On removal of the tourniquet the compressed tissue appeared white and lifeless, but twelve hours later it was with some difficulty that the slightly erythematous mark could be identified. The tissues during the amputation were firm and cold and of excellent color, and the blood was not clotted in the vessels.

A half-hour after being returned to the ward she took her full diet and appeared as though no operation had been performed. Unfortunately the loss of the leg caused her acute depression; she did not wish to live and soon began to resist taking fluids and nourishment. The stump did well, although it drained a moderate amount of pink serous fluid for four days. The patient's depression continued and, despite all efforts, bronchopneumonia developed on the fourteenth postoperative day and she died.

The following cases are cited for comparison of the effects on the patient of spinal anesthesia induced with procaine hydrochloride and anesthesia induced with the ice-tourniquet technic.

CASES 2 and 3.—On Sept. 23, 1942, 2 remarkably similar patients arrived at the hospital, both having dry gangrene of the distal third of the right foot. Both were in good general condition, one being a white man aged 78 and the other a Negro woman aged 82. Both patients received practically the same care while in the ward prior to operation. The man, slightly younger, was definitely the stronger. His temperature stayed below 99.6 F., while the woman's ranged a full degree higher. On September 28, the woman's right leg was placed in ice to the upper thigh, and a tourniquet was applied at the level of the tibial tuberosity. An hour later a tourniquet was applied to the mid thigh. She did not complain of discomfort but rather received relief from the ache of her dying foot. The following morning supracondylar amputations were performed on both patients by the same operator and team. The technic was as nearly as possible the same except that the man was given the routine medication preparatory to spinal anesthesia,  $\frac{1}{4}$  grain (15 mg.) of morphine sulfate,  $\frac{1}{20}$  grain (0.5 mg.) of atropine sulfate an hour before the intraspinal administration of 60 mg. of procaine hydrochloride. He withstood the operation fairly well although he was definitely depressed.

The woman, after her regular breakfast and needing no preoperative medication whatever, underwent the same procedure. She carried on a conversation during the whole operation and was distinctly surprised to find that her leg had been removed. Within an hour of returning to the ward the woman had eaten her lunch by herself, while the man refused all food except one mouthful of potatoes, after urging. During the afternoon he appeared mildly depressed and in somewhat of a daze and was unable to sit up in a chair. He refused his supper, which meant that he had had practically no food during the day. The woman was bright, sat up in a chair for two hours during the afternoon and ate her regular supper. She needed no postoperative sedation whatever, while the man required two  $\frac{1}{6}$  grain (10 mg.) doses of morphine sulfate during the afternoon and night. The postoperative course of the stumps was almost identical. The man's stump drained moderately for one day, while the woman's drained for three days. Both stumps appeared agglutinated by the fourth day; the woman's sutures were removed on the eighth day and the man's on the eleventh day postoperatively. At the time of writing both have comfortable, firm, well healed stumps. The man's temperature rose to 101 F. on the first two postoperative days, while that of the woman was normal with one elevation to 100.2 F. on the third day.

CASE 4.—A second opportunity to compare the two anesthetics occurred at about the same time. On Aug. 20, 1942 a 66 year old white Hungarian came to the hospital complaining of pain in his right foot of four months' duration. During this time he had received paraeæ treatments to both feet at another hospital. A month prior to his admission to the hospital an ulcer developed on the lateral border of the right heel, which resisted healing. The whole foot shortly became cold and bluish, and a second ulcer appeared on the dorsum. The foot was too painful to walk on and the patient was sent to the City Hospitals. Review of the family history showed that the patient's father died at the age of 58 from heart disease. His mother died at the age of 30 from an unknown cause. There was no history of diabetes in the family and no other significant findings. Before the onset of his illness the patient had been working in a bakery. He had had mild exertional dyspnea of late years.

Physical examination showed a thin white man who appeared physically older than his stated 66 years. The blood pressure was 150 systolic and 90 diastolic, the temperature 100.6 F., the pulse rate 108 and the respiratory rate 22. The skin was dry, loose and inelastic. There were scattered moist rales at the bases of both lungs. The size of the heart was within the upper limits of normal. There was advanced arteriosclerosis, and no pulse was

palpable in either foot or ankle. The right foot was cold and cyanotic, with one ulcer on the dorsum and another on the lateral aspect of the heel. The ankle showed a mild cellulitis. The urine was clear; the white blood cell count was 7,900, and the hemoglobin content was 105 per cent.

Warm saline compresses were applied to the ankle. The patient was given  $\frac{1}{4}$  grain (15 mg.) of papaverine hydrochloride every four hours in an effort to increase the blood supply to the foot. He received four lumbar sympathetic blocks with procaine hydrochloride during the first ten days, during which the threatening gangrene became definite, involving the distal third of the foot. The patient's general condition was good; he was taking his meals well and was able to be up in a chair and look after himself in many ways.

On September 10 a supracondylar amputation was performed. The patient was given the routine medication of  $\frac{1}{4}$  grain (15 mg.) of morphine sulfate and  $\frac{1}{120}$  grain (0.5 mg.) of atropine sulfate an hour before the spinal anesthetic of 60 mg. of procaine hydrochloride was administered. The operation was the standard one that is used routinely in this hospital for supracondylar amputations. During the operation the blood pressure dropped to 95 systolic and 60 diastolic but was restored to the preoperative level with vasoconstrictors.

After the operation the patient was extremely depressed, although not particularly more so than the average elderly patient after a major operation and spinal anesthesia. His depression, however, was emphasized when he was compared with patients who had had the same procedure with the ice-tourniquet anesthesia. What little he ate for forty-eight hours was hand fed. He was not able to sit up for two days but lay in a stuporous slump. His memory of this period was of a vague horrible dream. After forty-eight hours his strength gradually returned, and he went on to an uneventful recovery, the stump being well healed when he was discharged from the hospital sixteen days later.

During his last week in the hospital the other foot showed signs of embarrassed circulation, with coldness, cyanosis and tenderness. The patient insisted on leaving despite this new involvement, but four days later, on September 30, he returned with the toes and distal third of his remaining foot in an early gangrenous condition. The area was painful and very tender. His temperature was 98 F., the pulse rate 80 and the respiratory rate 20. The general physical condition had remained unchanged since his previous admission, and the stump was well healed, firm and not tender. He was treated as before, but definite dry gangrene of the toes and distal half of the foot developed. On the evening of October 7 the left leg was placed in the box and the induction of anesthesia by the ice-tourniquet method was begun. The patient had no discomfort except a mild ache for the first ten minutes of contact with the ice. He slept well and ate a full breakfast next morning. About 10:30 a. m. he was taken to the operating room and an operation identical to the previous one was performed by the same operator on his remaining leg. Throughout the operation the patient carried on a spontaneous conversation and complained of no pain whatever. The blood pressure remained perfectly even. As the operation was being finished he mentioned that he was hungry, and within fifteen minutes after leaving the operating room he had eaten a full soft diet by himself, while sitting up in bed. Two hours later, on his own suggestion and unassisted, he got into a wheel chair and visited friends about the ward. At no time, either preoperatively or postoperatively, did he receive or need any sedation. For twenty-four hours ice caps were kept on the stump, which drained a moderate quantity of sanguinous fluid for two days. Although healing was slightly slower than after the first amputation, the stump was well healed in two weeks and was firm and in good condition.

#### COMMENT

The details of our management of patients with arteriosclerotic gangrene depends on the urgency of their condition. If gangrene is well established in the foot with a spreading cellulitis and the patient is in a toxic condition, he obviously will benefit from an immediate physiologic amputation. Then for forty-eight hours general supportive measures can be carried out with the patient physiologically free of the offending limb. As a second phase of the treatment actual amputation is then performed with a more reasonable expectation of a satisfactory outcome. On the other hand, if there is no infection present and the patient is in relatively good condition amputation does not constitute an emergency, and if the ice-tourniquet technic is to be used in order to minimize the general operative depression it need be applied for only a few hours prior to the time for operation.

When the limb is first chilled it aches moderately for ten or fifteen minutes, but no patient has complained more than just to mention it. In cases in which there is severe pain from the gangrene, the ice affords a definite relief. The application of the tourniquet causes moderate discomfort also, but it is in no way excessive if the leg has been well chilled. All sensation from the knee down stops entirely within a few more minutes.

In every case the temperature of patients with only gangrene and spreading cellulitis fell to normal within twelve hours of the application of the ice-tourniquet treatment. By far the most dramatic and convincing factor of this whole management was the tremendous change for the better which occurred in the first twenty-four hours. To be convinced, it is necessary to see this change, since it is difficult to evaluate statistically. Suffice it to say that the improvement described in the first case has been duplicated many times.

In the six month period since the ice-tourniquet technic was first tried for the management of arteriosclerotic gangrene 20 amputations have been performed at this hospital, 7 with spinal anesthesia (60 mg. of procaine hydrochloride), 3 with intravenous pentothal sodium anesthesia and 10 with ice-tourniquet anesthesia. From the start it was evident to all concerned that the preoperative phase of this management had unquestionable value to the debilitated, toxic patient in desperate need of supportive measures before operation. The actual value of the ice-tourniquet procedure as anesthesia for the operation appeared more open to criticism. It was suggested that the preoperative chilling be used from the knee down and that the amputation be performed above the knee, with spinal anesthesia. In this way operation could be performed without a tourniquet, better hemostasis thus being permitted; the incision would be through "live, healthy" tissue which had not been deprived of its regular blood supply and chilled considerably below body temperature for several hours, and the necessity for hurrying the operation owing to a short lived anesthesia would be relieved.

It was with the intention of properly evaluating the aforementioned criticisms that the 20 amputations were classified as to the anesthesia used. The 3 patients receiving the intravenous anesthetic had each been prepared for ice-tourniquet anesthesia. In each case the anesthesia was poor because the arterial blood supply had not been occluded by the upper tourniquet.

The second phase of treatment, namely, the use of the ice-tourniquet technic to produce anesthesia, has received critical evaluation in this hospital as to its actual worth. At first there was a tendency to believe that eventually ice-tourniquet management would be reserved as a preoperative measure for patients in a critical condition and badly in need of supportive measures prior to operation. Then, after twenty-four or forty-eight hours, with the patient in a reasonably good condition, the amputation could be performed with the patient under low spinal anesthesia. Because of this belief, spinal anesthesia was used for amputations on relatively strong patients without complications. Patients for whom the ice-tourniquet management was started as a preoperative supportive measure were carried through the amputation under ice-tourniquet anesthesia. Actually it was the nursing personnel who called attention to the fact that the patients having their legs amputated under the ice-tourniquet anesthesia were much stronger and more cooperative postoperatively. It was pointed out that when spinal anesthesia was used frail patients were profoundly depressed for thirty-six or forty-eight hours after operation, while when the ice-tourniquet technic was used they had a relatively good appetite immediately postoperatively, moved about in bed to help

themselves and were able to sit up in a chair immediately. The contrast between the immediate postoperative reactions following the two types of anesthesia was noted again and again.

The increased drainage after amputations for which ice-tourniquet anesthesia was used was noted also by Allen. His explanation was that the chilling of the stump delays agglutination and so allows the fluid to drain out of the tissues. Supporting this statement is my observation that by the end of a week there is little if any difference in the appearance of the wounds whether the operation was performed under spinal anesthesia or done with the ice-tourniquet technic. In my short series the postoperative temperature took nine days, on the average, to return to normal after spinal anesthesia, as against only four and one-half days after ice-tourniquet anesthesia. Better drainage due to chilling may well be the reason for the difference.

I believe that the use of two tourniquets is a distinct advantage. The later application of the upper tourniquet allows the tissues through which the operation is performed to be washed free of and recover from the toxins which were being absorbed from the infected foot. This advantage is lost when only one high tourniquet is used.<sup>1</sup>

In a recent report of a case Schiebel<sup>6</sup> stated that for good anesthesia the tourniquet should be "just tight enough to restrict venous return, but not tight enough to interfere with arterial inflow." It must be emphasized again that in my experience satisfactory anesthesia was secured only when the arterial flow was definitely interrupted. It is rather surprising how much force is required to occlude the blood flow entirely in arteriosclerotic limbs.

#### SUMMARY

The ice-tourniquet treatment has a very definite place as a preoperative measure in the management of debilitated patients with gangrene.

Operative or postoperative reactions following the use of the ice-tourniquet method for anesthesia are slight compared with those following the use of spinal anesthesia.

The need for preoperative and postoperative sedation is practically eliminated.

The stump is apparently not harmed by the ice-tourniquet treatment, and healing is perfectly satisfactory.

The management of 4 cases is presented in detail. It is suggested that the use of two tourniquets with amputation between them, constitutes an improvement over the use of one tourniquet.

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# NERVE REGENERATION IN THE RAT FOLLOWING TUBULAR SPLICING OF SEVERED NERVES

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For many years a method for uniting severed nerves has been used in experiments in my laboratory which has proved so superior to the conventional suture methods that the possibility of adapting it to the surgical needs of human beings deserves serious consideration. While the studies pursued with this method have branched into many phases of the problem of nerve restoration, the following brief account will confine itself to those aspects which seem to be of immediate practical interest.

The method consists in splicing the stumps of a severed nerve by inserting them in a closely fitting sleeve of live artery. First devised for use in the frog and toad<sup>1</sup> the method was then applied to the rat<sup>2</sup> and has lately been used extensively in work on this animal. Save for a brief note,<sup>3</sup> no special description of the technic and of the processes of nerve regeneration following its use has as yet been given. This missing information will be supplied in the present paper.

It should be understood from the outset that the purpose of using an arterial link to reunite ends of a nerve is primarily to provide a firm tie between the stumps of a sort that will favor regeneration of nerve fibers and prevent formation of scar tissue. It is not intended as a means of bridging larger gaps in a nerve by providing regenerating fibers with a pipeline, as it were, for which purpose "tubulation" or "tubularization" of nerve stumps has been used, with varying success, in the past.<sup>4</sup> As nerve ends can never be strictly apposed in the microscopic sense and, in fact, for best histologic results never should be,<sup>5</sup> the function of the arterial tube as a guide for nerve fibers will also come up for consideration, but this is a secondary matter. The main purpose of use of the arterial sheath is to eliminate the need of suturing the stumps together, so that the various hazards to nerve regeneration inherent in ordinary methods of suturing may be avoided. Owing to the greater tensile strength of the arterial link as well as to some other advantages to be discussed in subsequent paragraphs, tube splicing seems to be

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1. Weiss, P.: Selectivity Controlling the Central-Peripheral Relations in the Nervous System, *Biol. Rev.* **11**:494-531, 1936.

2. (a) Sperry, R. W.: The Effect of Crossing Nerves to Antagonistic Muscles in the Hind Limb of the Rat, *J. Comp. Neurol.* **75**:1-19, 1941; (b) Transplantation of Motor Nerves and Muscles in the Forelimb of the Rat, *ibid.* **76**:283-321, 1942. (c) Weiss and Campbell: Unpublished data.

3. Weiss, P.: Re-Union of Stumps of Small Nerves by Tubulation Instead of Suture, *Science* **93**:67-68, 1941.

4. Stookey, B. P.: Surgical and Mechanical Treatment of Peripheral Nerves, Philadelphia, W. B. Saunders Company, 1922. Pollock, L. J., and Davis, L.: Peripheral Nerve Injuries, New York, Paul B. Hoeber, Inc., 1933.

5. Nageotte, J.: L'organisation de la matière dans ses rapports avec la vie, Paris, F. Alcan, 1922.

superior, on the whole, to the only other sutureless technic of nerve union, the blood plasma technic of Young and Medawar.<sup>6</sup> However, there will be situations in which arterial splicing is not practicable while plasma suture is.

The adequacy of the arterial link has been proved both with regard to its mechanical function of tying and holding the nerve ends together and with regard to its capacity to provide most favorable conditions for the outgrowth of regenerating fibers from the proximal stump and the invasion of the peripheral stump. The main advantages are as follows:

1. Clotting blood plasma and tissue fluid seal the arterial sleeve tightly to the surfaces of the inserted nerve ends. As adhesion is proportional to the size of the adhering surfaces, the tensile strength of an arterial juncture, with the outer wall of the nerve and the inner wall of the artery in extensive contact, is naturally much greater than that of end to end blood plasma fusion, as practiced by Young,<sup>7</sup> just as two threads glued lengthwise to a common third thread are more firmly united than if they were merely joined end to end.

2. The arterial link permits, without loss of holding strength, leaving a slight gap between the nerve ends, which seems to be beneficial to smooth nerve regeneration.

3. The introduction into the nerve of a foreign body, such as catgut, silk or nylon, is avoided. This not only precludes the foreign body reactions common in such cases but, more significantly, eliminates the disorientation effects which suture threads exert on the regenerating nerve fibers in their vicinity.

4. Longitudinal stresses, which would otherwise be taken up by the unelastic suture threads, are transmitted through the tissue matrix filling the gap between the two cut ends and force that matrix into longitudinal orientation, which, in turn, imparts corresponding orientation to the regenerating nerve sprouts.

5. As a corollary of the preceding statement, the disorientation commonly observed in the so-called scar region is prevented, which reduces the incidence of fiber branching and of formation of local neuromas to insignificant proportions.

6. The uninterrupted canalization between the two nerve stumps prevents both the escape of bundles of nerve fibers into the surrounding tissues and the ingrowth of scarifying fibrous tissue into the wound.

7. Branching and diffusion of fibers at the suture level thus being avoided, conditions are more favorable for an orderly point to point reconnection between central cells and peripheral organs than is common in nerve regeneration. This, in turn, must be expected to have important bearings on functional restoration. Instead of allowing fiber branches to scatter widely all over the peripheral stump, the arterial sleeve insures the preservation of some degree of topographic localization throughout the process of regeneration.

8. Arterial splicing makes it possible to mend small nerves for which ordinary suturing would not be feasible.

In support of these statements, I shall present the results of a thorough histologic study of 23 sciatic nerves of rats spliced with arterial segments, 10 of which were studied in regularly spaced cross sections while 13 were studied in serial longitudinal sections. On 8 of the transversally cut nerves complete fiber counts through representative regions, old and regenerated, were made. Moreover, most

6. Young, J. Z., and Medawar, P. B.: Fibrin Suture of Peripheral Nerves, *Lancet* 2:126-128, 1940.

7. Young, J. Z.: The Functional Repair of Nervous Tissue, *Physiol. Rev.* 22:318-374, 1942.

animals before being killed were subjected to physiologic tests in which the isometric tension produced by the gastrocnemius muscle on stimulation of the regenerated sciatic nerve was recorded.

#### TECHNIC

While many kinds and sizes of nerves have been used, the following description will be confined to the suture of the sciatic nerve in rats of between 200 and 300 Gm. body weight. Arteries of proper diameter are furnished by the trunk aortas of smaller animals and the carotid and femoral arteries of larger animals. The artery which appears in all figures 1 *B* to 7 of this report is a segment of aorta.

The sciatic nerve is severed in the proximal part of the thigh, either at the level where it is still uniform or at a more distal level, where it is already internally subdivided into a peroneal and a tibial branch. After transection the two ends of the nerve are inserted into an arterial sleeve previously prepared in the following way. A segment of artery about 1 cm. in length is transferred into Ringer's solution, where it is freed from its blood content by gentle squeezing. A specially designed splicing forceps is then introduced into the empty lumen. The procedure is illustrated in figure 1 *A*. The splicing instrument consists of a forceps terminating in two half-cylinders, which when closed form a tube. Into this fits a solid core of conic shape (fig. 1 *A, a*). For use on smaller nerves the half-cylinders are fashioned by grinding down hypodermic needles of suitable gage. These are then soldered to the prongs of a steel forceps. For greater rigidity the proximal part of the needle is filled with solder. Both halves are so adjusted that when the forceps is closed they will meet edge to edge. Since the base of the conic core has the same diameter as the outside of the tube, the closed forceps and the inserted core form a continuous tapering rod. In this position the instrument is introduced into the artery, as shown in figure 1 *A, b*. From the tapering core the arterial fragment is then pulled over the cylindric end of the closed forceps, whereupon the core is withdrawn and the forceps slightly opened so as to distend the artery (fig. 1 *A, c*). Since in the case of thick-walled arteries the spring of the forceps may not be sufficient to produce distention, it is advisable to fasten a setscrew between the two prongs of the forceps, the turning of which can force the branches apart. The open forceps is then slipped over one of the nerve stumps so that the cut end will come to lie between the two prongs inside the widened orifice of the arterial sleeve. After the nerve end is clutched by closing the forceps, the arterial fragment is pulled back from the forceps over the nerve, as shown in figure 1 *A, d*. When the forceps is withdrawn, about one half of the length of the sleeve is left over the nerve end while the other half is empty (fig. 1 *A, e*).

To introduce the other nerve end into this empty part, an instrument illustrated in figure 1 *A, f* and called the "spreader" is used. It consists of a clip fashioned from an elastic wire band and acting like a forceps with reversed tips. When this clip is closed by lateral pressure with a needle holder, the two free end pieces are brought in apposition and can then be easily inserted into the open end of the artery. On release, the spring of the instrument opens the artery, as shown in figure 1 *A, g*. By appropriate bending of its apex, the elasticity of the instrument can be adjusted so as to distend the artery to just the desired amount. The nerve stump is then introduced into the opening and pushed on until it meets the previously inserted stump. When the spreader is withdrawn, the released artery by its elasticity clamps down on the second nerve stump. The surfaces of the spreader must be polished, for rough edges tend to pull the nerve out again. The grip of the arterial sleeve on the two nerve ends is then tightened by stretching the artery lengthwise with two pairs of forceps. This secondary elongation entails



a slight separation of the formerly closely apposed cut surfaces, as is shown in figure 1 *A, h*. However, such a small gap, measuring in length not more than the diameter of the nerve, is not detrimental but apparently even favorable to smooth crossing of the regenerating fibers from the proximal into the peripheral stump.

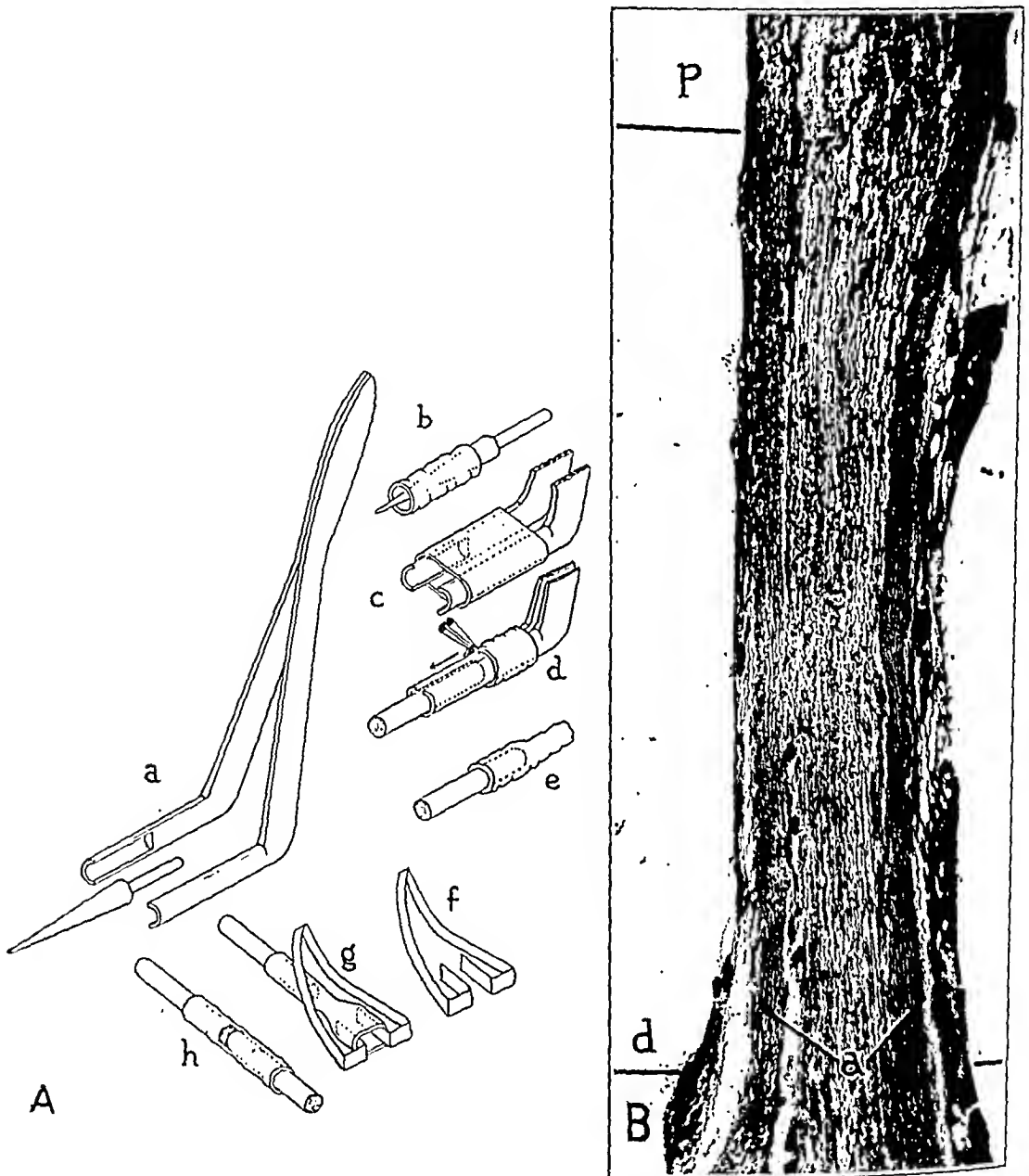


Fig. 1.—*A*, splicing technic. An explanation is given in the text. *B*, longitudinal section through regenerated sciatic nerve spliced with arterial sleeve, at transition from proximal (*p*) to distal (*d*) stump, one hundred and fifty days after operation ( $\times 41$ ). *a*, wall of artery (note lamination).

During the operation the wound bed may be irrigated with Ringer's solution, which prevents the sticking of the instruments to the tissues. The splicing should not be done until intraneural bleeding from the cut section has ceased. In fact,

if there should be secondary bleeding into the gap between the two stumps after the splicing, it is indicated to withdraw the peripheral stump from the sleeve again, remove the blood clot and resplice. The effects of plasma clots left between the stumps are being further investigated and will be reported in a later communication.

After the splicing, all excess fluid is blotted or sponged from the surroundings. Leaving the exposed area to dry for several minutes results in a firm tie between the wall of the artery and the inserted nerve stumps. Residues of blood plasma along the inner wall of the artery obviously help in cementing the union. That this is not absolutely essential for successful splicing, however, is demonstrated by the fact that arteries kept in Ringer's solution on ice for one or two days are quite adequate, although their inside is much more slippery than that of fresh artery. When these are used, the clotting of the fresh tissue juice along the sticky surface of the nerve obviously provides the sole cementing agent. The wound may then be closed. Experiments with prolonged exposure show that after fifteen minutes the tie has become firm enough to withstand moderate tension. Pending more exact determinations of the tensile strength of arterial joints at various intervals after the operation, it may be stated that in some test experiments in which the wound was opened a few hours after the operation noticeable pull was required in order to break the link between the two nerve stumps. Since the adhesive power between arterial wall and nerve surface is proportional to the extent of surfaces in contact, and hence to the length of the arterial sleeve, the latter will have to be made the longer the more tension the spliced nerve is expected to sustain.

#### HISTOLOGIC OBSERVATIONS

A number of typical examples may serve to illustrate the type of nerve regeneration obtained with arterial splicing. Fixation in Bouin's fluid under stretch and impregnation with silver salts according to the method of Bodian, sometimes supplemented by staining with Mallory-azan stain, have been used throughout.

Figure 1 *B* presents a longitudinal section through the region of a splice one hundred and fifty days after the operation. The proximodistal direction is indicated in the picture. The central mass of nerve fibers can be seen to be bounded on either side by the laminated arterial wall. The seven to eight layers of elastic tissue forming this wall can be clearly recognized. The levels of the original cut surfaces can be reconstructed from the extent of the original epineurium of the nerve stumps. Since the perineurium and epineurium have failed to regenerate, their margins indicate approximately the farthest extent of old nerve. These levels are marked in the figure by solid lines. Between them the nerve fiber masses are devoid of epineurium and sheathed directly by the arterial sleeve. This region then corresponds roughly to the former gap. Since there may have been some slight retraction of the epineurium on either side of the gap, the original distance between the nerve ends may not have been quite as large as it would seem from the final picture. At any rate, this is the region which corresponds to the so-called scar region, or suture line, of a nerve sutured by ordinary methods. It can be seen from the picture that in this area the nerve is attenuated. This is due in part to the absence of the epineurium and in some measure to the smaller size of the nerve fibers. As will be shown later, however, it does not express a significant decrease in the number of fibers.

Several striking features of the regenerated nerve become obvious at once. The nerve fibers run in a straight course and in parallel orientation from the

proximal stump into the gap region, continue without deflection or confusion through this region and pass on straight into the peripheral stump. Nowhere is there evidence of the profuse branching, straying about and intermingling of fibers commonly observed at the transition from the proximal to the peripheral stump of nerves sutured by ordinary methods.

Figure 2 gives an enlarged view of the transition from the gap region into the peripheral stump of the same nerve as in figure 1 *B*. The entrance into the old peripheral stump is marked by the appearance on one side of the picture of the old epineurium; on the other side some fat tissue has penetrated. The central part of the picture is taken up by the strands of regenerated nerve fibers. These form a compact mass, packed about as densely as they are in normal nerve. They



Fig. 2.—Same preparation as in figure 1 *B* at transition from "gap" to peripheral stump ( $\times 115$ ); *a*, arterial wall; *p*, perineurium.

follow a well oriented straight course. Their size varies from very thin to relatively large fibers. In estimating size of fibers it must be remembered that with the methods of fixation and impregnation used in these studies large axis-cylinders collapse in many places along their course, which gives them the appearance of a string of beads, each myelin segment showing several constrictions. A further discussion of size of fibers will be presented later.

To either side of the nerve mass one sees spaces filled partly with vascularized fat tissue and partly with loose connective tissue, the extent of the latter being exaggerated by shrinkage during fixation. These layers separate the nerve core from the wall of the artery, which can be recognized by the characteristic lamination of the elastic tissue. Lack of intimate contact between the nerve fibers and the

inner wall of the artery is a frequent occurrence near the original arterial openings, where the epineurium and adhering loose connective tissue were tucked into the artery. In many spliced nerves, of which the present one is a typical example, there has been a definite tendency of this tissue to become converted into fat tissue, which then has remained interposed between the arterial wall and the surface of the nerve. Whether the breakdown of myelin with the liberation of phospholipids in this region has anything to do with this transformation into fatty tissue remains a matter for speculation. At any rate, this process remains localized about the ends of the sleeve, while in the intermediate zone close contact between the nerve fibers and their arterial container is preserved. This is further illustrated by the study of cross sections.

Figure 3 shows cross sections through a spliced and regenerated sciatic nerve one hundred and eighty-one days after operation at five different levels. The location of these levels is indicated in the accompanying diagram (fig. 3 *F*). The nerve had been transected at a level distal to its bifurcation into the tibial and peroneal divisions. Section *A*, through the proximal stump near the proximal end of the arterial sleeve, shows the two nerves with their perineuriums, surrounded by the artery. Some fat tissue can be seen wedged between the old epineurium and the arterial wall. This level is still more than 2 mm. proximal to the original level of transection. Yet the tibial nerve (lower left) gives evidence of being composed largely of regenerated fibers. In contrast, the peroneal division (upper right) shows essentially the organization of normal nerve, although it, too, contains a certain contingent of regenerated fibers. The situation is explained by the fact that ascending traumatic degeneration following transection of a nerve may extend several millimeters centrad from the wound, so that regeneration actually starts from a level slightly proximal to the actual level of sectioning. The difference between the peroneal and the tibial nerves in this case is simply due to the fact that after transection the latter has retracted a little farther in its sheath (fig. 3 *F*). Section *B*, which lies 2.5 mm. distal to *A*, shows the end of the proximal stump of the peroneal nerve, while the fibers of the tibial nerve at this level have already entered the gap between the original stumps. Consequently, the peroneal nerve (in the center) is still surrounded by some of its perineurium, while the fiber masses emerging from the tibial nerve (on the left) are applied directly to the inner wall of the artery. Section *C*, which is 2 mm. distal to section *B*, lies entirely within the gap region, and here the fiber bundles fill the lumen of the artery completely, except for a small extension of vascularized fat tissue on the right.

This is, then, the aspect in cross section of the fiber masses between their emergence from the original proximal stump and their entrance into the original distal stump; in other words, the suture line corresponding to the scar region of ordinary nerve sutures. The fibers can be seen arranged in small bundles, typical of regenerated nerve, with some larger spaces in between. It will be noted that nearly all fibers appear hit in their cross section and that practically none course in the plane of sectioning. This is merely another expression of the straight, parallel, longitudinal orientation of the regenerated fibers. Section *D*, 2.5 mm. distal to *C*, is from the region of the old peripheral stump of the tibial and peroneal nerves, still inside the arterial sleeve. Both nerves are completely refilled with nerve fibers, surrounded by their old perineurium and again accompanied by fat tissue, as previously discussed. Section *E* introduces a still farther distal level, 10 mm. from *D*, where each nerve has become subdivided into branches. Except for a few blank spaces, these branches have received their full complement of nerve fibers, and, as can be seen, many of these fibers have assumed fairly large diameters.

Figure 4, finally, gives details at higher magnification from sections 3 *A*, *C* and *D*, respectively. Except for an occasional straggler coursing obliquely or transversally, the vast majority of fibers can be seen to be oriented perpendicular to

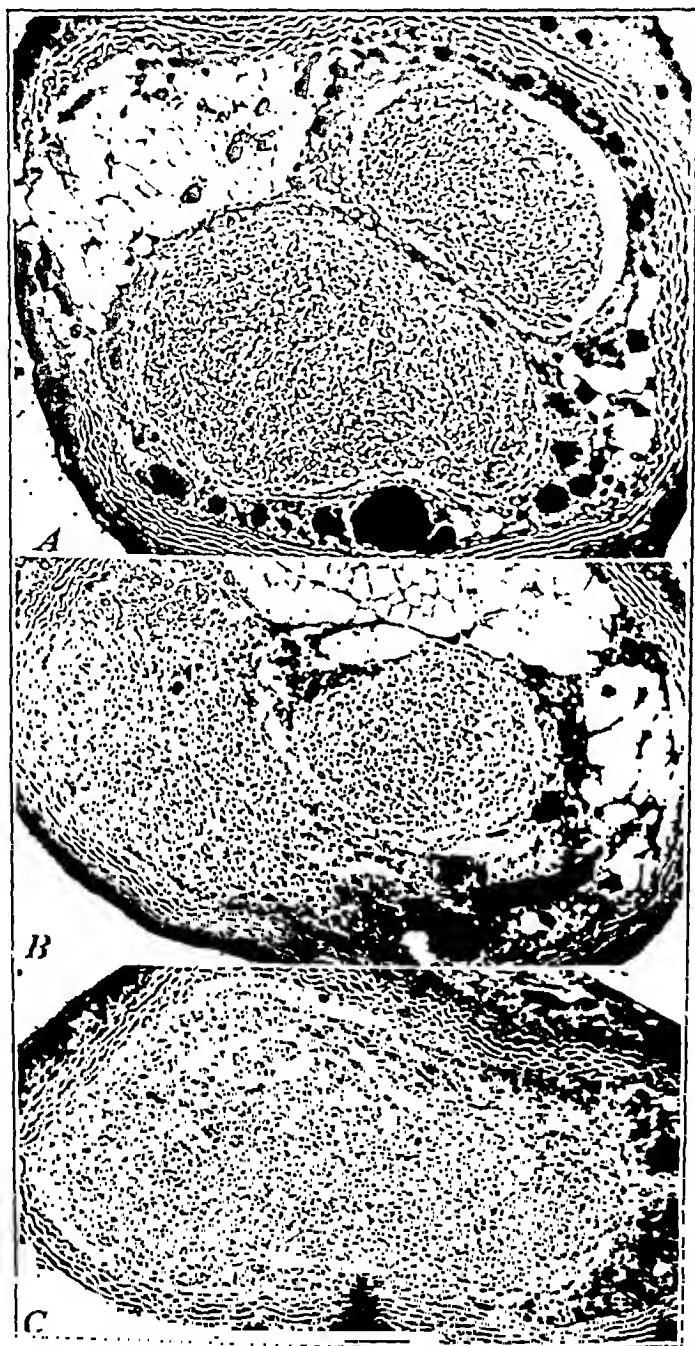


Fig. 3.—Cross sections through an artery-spliced and regenerated sciatic nerve one hundred and eighty-one days after the operation. Further explanation is found in the text ( $\times 62$ ).

the plane of sectioning, i. e., parallel to the axis of the nerve. A comparison of the middle section, which runs through the gap region of the nerve splice, with the other two sections reveals that on the whole the reorganization of the nerve is somewhat further advanced inside the old stumps, both central and peripheral,

than it is in the intervening zone. In the latter the fibers are more loosely packed, there is a somewhat greater proportion of endoneurial tissue and there seem to be fewer fibers of the largest caliber. It would seem, therefore, that in the peripheral stump, where the fibers had the benefit of traveling inside the old



Fig. 3.—(Continued).

degenerated Schwann sheaths, reorganization and maturation took place at a slightly faster rate than in the pathless area of the gap. Sections from other spliced nerves confirm this impression. However, it will require more intimate studies to determine whether the observed differences are significant.

With regard to size of fibers, a striking difference exists between the old fibers in the proximal stump and their regenerated peripheral parts, as seen in figure 3 B

and C. The left upper half of figure 3 A shows a sector of the original fiber complement of the peroneal nerve. While many of these fibers were hit slightly obliquely and therefore appear somewhat larger, most of them, particularly toward

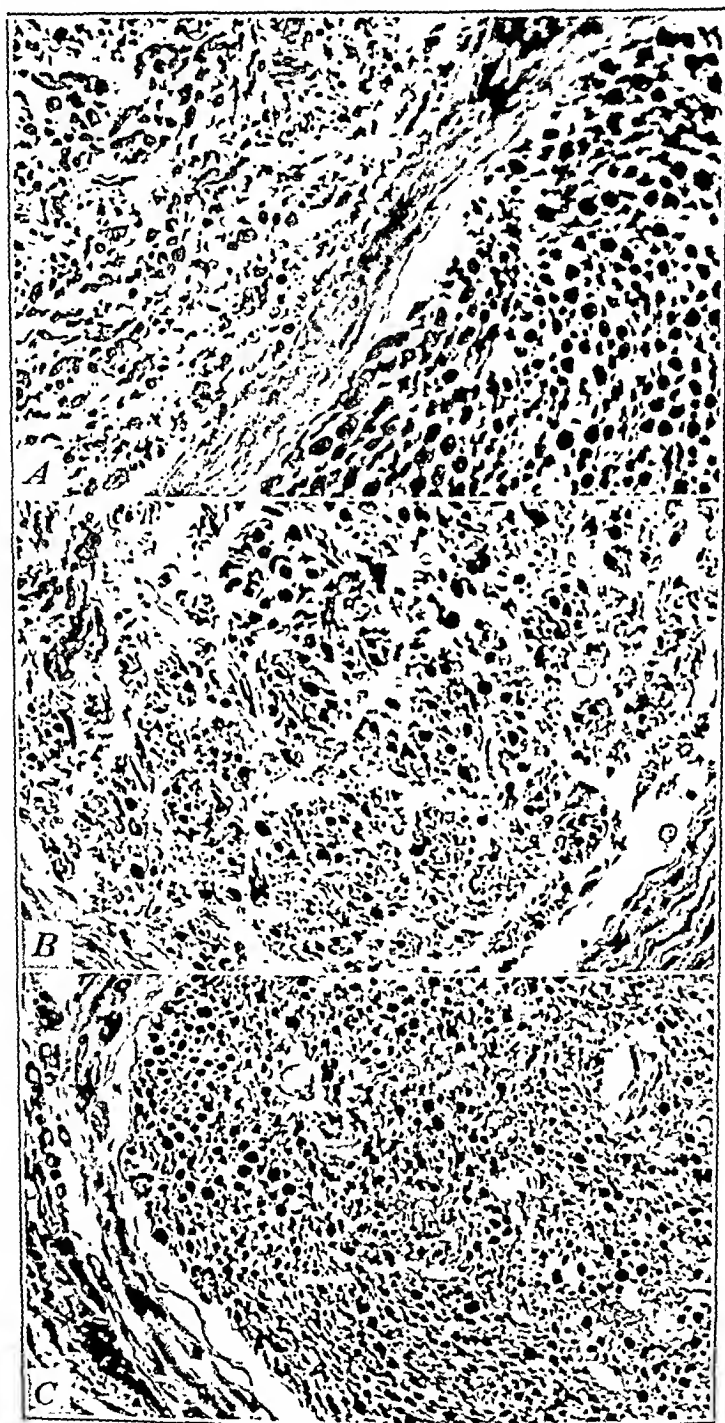


Fig. 4.—Details from cross sections A, C and D of figure 4 ( $\times 210$ ).

the center of the nerve, appear in straight cross section. As one can readily see, the proportion of large diameter fibers in this old nerve is much greater than is to be found at any one of the more distal levels. It is well known that the newly

regenerated branches, growing out from a severed central stump, are all very thin fibers of more or less equal diameter. It is only secondarily that the peripheral parts of some of the regenerated fibers will grow in thickness, tending toward the restoration of the differentials of fiber size existing in normal nerves. How closely the original pattern of size distribution is restored and to what extent the resumption of a definite caliber is controlled by the origin of the fiber branch, the path it has taken, the length it has attained and the termination it has reached have not yet been systematically investigated, although some occasional attention has been given to the problem. However this may be, it is obvious that in the present nerve the fiber composition of the peripheral trunk has not yet been fully restored to its original condition in six months after the transection. By far too many fibers are still in the small and very small classes, with fibers of the larger caliber comparatively scarce.

All other nerves studied on which the operation was performed properly conform to the type of regeneration just described. In all of them the nerve fibers have retained their straight longitudinal course throughout the gap and peripheral stump. Occasionally single fibers or small bundles do run off at an angle for short distances, but these occurrences seem to be negligible when contrasted with the strict longitudinal orientation of the bulk of the fibers. Perineurium and epineurium have not regenerated, and within the stretch intervening between the original cut levels the fibers are in direct contact with the inner surface of the arterial sleeve, which within this area, then, serves as nerve sheath.

The vascular supply of the regenerated nerves is partly intraneural, with most vessels running lengthwise inside the nerve, and partly perineural, with accessory vessels from the interstitial fat tissue entering the nerve.

#### FIBER COUNTS

Counts were made of the number of nerve fibers seen in cross sections of 8 of the nerves operated on.<sup>8</sup> Data for 5 of these, for which complete counts are available through all three critical levels, i. e., through proximal stump, gap and distal stump, are included in the following tabulation. The remaining 3 counts are incomplete in that no enumeration was made at the level of the gap, and these are therefore omitted.

The counts were made according to the method regularly used in this laboratory in the past.<sup>9</sup> The margin of error of this method was found in earlier observations to lie below 2 per cent for fibers stained for myelin<sup>10</sup> and within 6 per cent for silver-impregnated fibers.<sup>9</sup> In view of the large number of very fine fibers present in newly regenerated nerve, increasing the difficulty of identification, the counting error may be considered higher in the present tabulations. The results are summarized in the table.

The most striking point is the close correspondence between the number of fiber sections counted in the old proximal stump of the sciatic nerve and the number of regenerated fiber sections within the gap area. Only in nerve *B* does the gap show a deficit of nearly 20 per cent, and this is readily explained by the fact that in this experiment the artery had in one place sustained a break, through which

8. Dr. Raymond Litwiller assisted in making the fiber counts.

9. Litwiller, R.: Quantitative Studies on Nerve Regeneration in Amphibia: I. Factors Controlling Nerve Regeneration in Adult Limbs, *J. Comp. Neurol.* 69:427-447, 1938.

10. Weiss, P.: Further Experimental Investigations on the Phenomenon of Homologous Response in Transplanted Amphibian Limbs: II. Nerve Regeneration and the Innervation of the Transplanted Limbs, *J. Comp. Neurol.* 66:481-535, 1937.



a mass of fibers escaped into the surroundings so as to be lost for the count. In all other instances the difference between the two levels lies within the limits of the error inherent in the method. These figures, therefore, bear out completely the evidence of the histologic observations, according to which, on the whole, each fiber of the proximal stump has during its regenerative outgrowth remained single, without bifurcation. The fiber counts inside the distal stump show a distinct drop below those of the gap, varying with the distance at which the count was taken. This drop can be accounted for by the branching off from the main nerve trunks of some small fiber bundles which were omitted in the distal counts. That the decline is not necessarily an expression of incomplete regeneration is demonstrated by the fact that even in the youngest splice (*A*), studied seventy-four days after the operation, the distal stump has become fully repleted.

#### FUNCTIONAL OBSERVATIONS

While the relation between morphologic regeneration and functional recovery will be more fully discussed in a subsequent paper, a few remarks on the subject seem in place. Obviously the stage has been passed when one can acquiesce in

*Results of Fiber Counts*

Nerve	Days After Operation	Number of Fibers			Length of Gap, Mm.
		Proximal Stump	"Gap"	Distal Stump	
A.....	74	5,415	5,240	5,210	3.5
B.....	137	5,235	4,245*	3,218	4.5
C.....	143	4,435	4,855	4,075	Undetermined
D.....	153	4,613	4,770	3,425	2.0
E.....	172	5,590	5,545	4,695	Undetermined

\* Break in arterial wall with extensive escape of fibers.

such general statements as that function has become "improved" or "partially restored" or has remained "abnormal." Neither sensory nor motor functions are in themselves entities; they are complex phenomena in which each phase is differentially affected by denervation and nerve regeneration. For each phase definite criteria must be established, and functional restoration must then be described in terms of these criteria. On the motor side restoration of trophic influences, electric excitability, transmissibility at the myoneural junction, reflex action, muscular power and, finally, coordination must be given separate consideration in relation to nerve regeneration. As for the restoration of muscle power, an adequate test consists of determining the maximum tension which the reinnervated muscle can produce on direct stimulation as well as on indirect stimulation through its nerve. Registered isometrically, the tension developed after direct stimulation of the muscle is a measure of the amount of functionally adequate contractile tissue, while isometric tension developed in the muscle after electric stimulation of its nerve with supramaximal shocks gives a measure of the fraction of total contractile tissue which has become reinnervated.

In the experiments with the best results, the maximal tension obtained from a gastrocnemius muscle reinnervated from a spliced sciatic nerve was approximately equal to that recorded from the opposite gastrocnemius muscle, with undisturbed

innervation.<sup>11</sup> This means that the muscle on the side operated on either had suffered only a minor denervation atrophy or else had become restored to its original size after reinnervation. In such instances, tensions developed after supra-maximal stimulation of the nerves were likewise nearly symmetric on the two sides, proving that all of the muscle fibers in contractile condition had received reinnervation. This condition was found as early as ten weeks after splicing. This is remarkable, inasmuch as histologic preparations of these nerves reveal that most of the regenerated fibers are still rather immature, i. e., of small diameter with myelination in its early stages. In other words, the power developed by a motor unit does not depend on the state, size and degree of maturity of the efferent neuron provided neuromuscular transmission is established at all. This, of course, merely expresses the all or none nature of the contraction of muscle elements activated by nerve excitation.

In several instances, however, in which the histologic picture of the sciatic nerve as well as the fiber counts proved that the neurotization of the peripheral stump was fairly complete, the muscle power on the side of the operation, nevertheless, remained definitely deficient. Inasmuch as in most of these instances a comparison of tensions developed after direct and indirect stimulation showed that no major part of the muscle had failed to receive innervation, the weakness must be ascribed to permanent atrophy rather than to incomplete reinnervation. Such atrophy is usually evident to gross inspection, and quantitative determinations have not as yet been made. In the case of nerve B of the table, for instance, in which in spite of a sizable escape of fibers, a good two thirds of the original fiber complement of the proximal sciatic stump was found present in the distal branches at the knee, the gastrocnemius muscle was able to produce only between 10 and 20 per cent of the tension of the opposite, normal, muscle. Why the atrophy goes further in some instances than in others has not yet been determined. It is obvious that the atrophic condition of the muscles does not reflect on the number of fibers regenerated inside of the nerve stump but merely limits the number of terminal branches that will be produced inside the muscle. It is the average size, rather than the average number, of motor units that is reduced in such cases.

Return of muscle power was not paralleled, however, by return of coordinated function. While the return of sensitivity progressed gradually, as evidenced by the increasing reactions of the animals to nociceptive stimuli, motility of the legs remained inadequate. Motor responses consisted of generalized contractions of the several muscles of the leg, rather than of coordinated movements with muscles in orderly well timed operation. In general, the limbs after reinnervation behaved much as those described by Sperry<sup>2a</sup> after crossing peroneal and tibial nerves. Reciprocal contraction of antagonists is absent, and most responses are characterized by the prevalence of rigid plantar flexion. Sperry ascribed this incoordination to the fact that not all muscles innervated by either the peroneal or the tibial division normally operate in phase. Therefore, random redistribution of the nerve fibers of both nerves during regeneration must result in simultaneous contraction of muscles which originally were engaged independently. Since the rat is definitely incapable of any reeducation of its motor apparatus which might serve

11. The use of the side not operated on as control is somewhat objectionable, since Tamaki (Tamaki, K.: Further Studies on the Effect of Section of One Peroneal Nerve of the Albino Rat on the Intact Nerve of the Opposite Side, *J. Comp. Neurol.* 64:437, 1936) has shown that unilateral transection of the peroneal nerve in the rat depresses the growth of the peroneal nerve of the opposite intact side. Allowance must therefore be made for the fact that the "control" nerve is itself slightly reduced. Whether the muscle suffers correspondingly has never been determined.

to correct inadequacies produced by nerve crossing or other irregularities of the peripheral nerve distribution,<sup>12, 13</sup> no improvement in the incoordinated condition of the motor responses was to be expected.

A similar explanation may be advanced for the lack of coordination in the present experiments, assuming that a large proportion of the regenerated nerve fibers have come to terminate on muscles other than the ones with which they had originally been connected. This disarrangement of central-peripheral connections was not precluded by the fact that, as one can see from the histologic studies, the regenerating fibers have essentially retained their mutual topographic relations while traversing the scar and passing on into the peripheral stump. For any degree of rotation of the peripheral stump in regard to the proximal stump in the act of splicing must have produced a corresponding distortion of the pattern of peripheral nerve distribution relative to the original pattern and thereby entailed the functional confusion of which the observed incoordinated activity was an expression. In man, in whom the well marked fascicular topography of the nerve furnishes better landmarks for the orientation of the stumps than is available in the nonfasciculated nerves of the rat, a more congruous opposition of nerve sections, such as was advocated, for instance, by Stoffel (Vulpinus and Stoffel<sup>12</sup>), would be easier to achieve. It should be remembered, however, that many neurosurgeons do not believe such careful matching of the nerve surfaces to be necessary and that actually in man reeducation, in the sense of a reorganization of the central impulse patterns, might remedy the inadequacies resulting from altered peripheral connections, for which the rat, as has already been stated, has no remedy.

#### FAILURES

While the arterial splice when properly performed creates the most favorable conditions for smooth and unimpeded nerve regeneration, improper handling of the method may lead to failures just as severe as though no union of the stumps had been attempted. It has been well known since the work of Cajal<sup>13</sup> that even when the stumps of a severed nerve are left separated a trickle of nerve fibers from the proximal stump will finally find its way into the peripheral stump. The mechanism of this reunion, originally postulated to be chemotropic, was suggested by Dustin<sup>14</sup> to be haptotropic, and recent experiments<sup>15</sup> have furnished evidence that it is really a matter of contact guidance, rather than of attraction over a distance. Those nerve fibers which happen to strike on a peripheral degenerated nerve tube of modified Schwann cells form an adhesive surface for other nerve fibers growing out later, so that gradually an oriented path between the proximal and the peripheral stump is established. However, since the pioneering fibers have to traverse the relatively dense connective tissue of the scar and since this tissue does not seem to offer particularly favorable conditions for their growth, regeneration under those conditions remains always quantitatively inferior.

Exactly the same situation prevails when one of the stumps of a spliced nerve escapes from the sleeve. The sleeve, if it does not collapse entirely, becomes

12. Vulpinus, O., and Stoffel, A.: *Orthopädische Operationslehre*, ed. 3, Stuttgart, F. Enke, 1924.

13. Ramón y Cajal, S.: *Studien über Nervenregeneration*, Leipzig, 1908.

14. Dustin, A. P.: *Le rôle des tropismes et de l'odogénèse dans la régénération du système nerveux*, *Arch. de biol.* 25:269, 1910.

15. Weiss, P.: (a) *Nerve Patterns: The Mechanics of Nerve Growth*, *Growth (supp.)* 5:163-203, 1941; (b) *In Vitro Experiments on the Factors Determining the Course of the Outgrowing Nerve Fiber*, *J. Exper. Zool.* 68:393-448, 1934.

invaded by fibrous connective tissue no more advantageous for regenerating nerve fibers than ordinary scar tissue. Similarly, any break in the wall of the artery in the region of the splice impairs regeneration in a double way. In the first place, it permits the escape of fibers into the surroundings and, secondly, it opens the interior to the ingrowth of connective tissue from the vicinity of the nerve, which, in turn, leads to progressive fibrosis and strangling of the nerve fibers inside. A break in the arterial wall may be due to accidental injury during the operation or to later erosion of the wall as a result of infectious or autolytic processes. An example of each of these types is presented in figures 5 and 6.

Figure 5 shows the effect of a stab wound in the arterial wall made at the time of the operation. Owing to the lack of regenerative capacity of the artery this wound has remained open and has seriously affected the regenerative



Fig. 5.—Effect of a leak in the arterial wall on regeneration of nerve fibers, thirty-eight days after operation. An explanation is found in the text ( $\times 82$ ).

process of that area. Not only have the superficial fibers coming up along the perforated side of the wall escaped, but even deeper fiber masses have been deflected toward the leak. The picture one obtains in these cases resembles that of a streaming liquid escaping through a hole in the wall of a tube. Just as in the latter case eddies form—in the vicinity of the leak, so in the case of the nerve an extensive area of disturbance is set up within a certain radius of the opening, and in this area the nerve fibers leave their longitudinal course and converge on the hole. The mechanics of this disruption of the nerve pattern are apparently as follows: Blood plasma and lymph seeping through the hole after the operation coagulate in the direction of the flow and thereby establish a pathway into which the regenerating fibers may turn when they arrive at this level. Ingrowth of connective tissue from the outside along this same pathway, more-

over, produces a lateral adhesion, the tension of which further accentuates the local disorientation. Since nerve fibers have been demonstrated to follow such oriented pathways,<sup>16b</sup> a permanent outlet for part of the regenerating fibers is thus established.

Aside from distracting nerve fibers from their straight course, perforations are harmful in that they permit the invasion of fibrous tissue, which eventually establishes sclerotic islands inside the nerve. These, in turn, tend to choke nerve regeneration. While more detailed studies on the subject would be desirable, even our casual observations to date leave no doubt but that nerve fibers which lie embedded in this fibrous tissue remain very thin and immature. Even well oriented fibrous tissue is less pervious to nerve fibers than either degenerated nerve or the exudate of purely neural origin which fills the gap between the two stumps inside a well sealing arterial tube. Besides being a poor growth medium for nerve fibers, fibrous tissue may also be detrimental to the later functioning of nerve fibers contained in it, in that its progressive condensation may set up a pressure block interfering with conductivity.

In a good splice it is evidently the uninterrupted elastic layers that render the arterial wall escape-proof for nerve fibers. While in most experiments the arterial sleeves have retained their original texture throughout their length, a few have been observed in which circumscribed parts of the arterial wall had undergone more or less extensive dissolution. This may assume the aspect of either a local erosion from the outside or a gradual loosening up and swelling of the layers of the wall, with cells from the surroundings penetrating into the spongy mass. Whether these lesions are due to abrasions suffered in the operation or to infection cannot be said. At any rate, within these regions the arterial wall becomes porous, and as a result the pattern of nerve regeneration in such a region becomes thoroughly confused. Evidently, the porous condition of the wall, with the resulting transudation of tissue fluids and the release of longitudinal stress, causes again a widespread disorganization of the matrix inside the arterial lumen, within which the new nerve sprouts grow out, and this entails a complete disorientation of the nerve fibers in that vicinity.

Figure 6A shows a tangential section in the longitudinal direction of the nerve through one such area. The middle portion of the picture shows criss-crossing nerve fibers, many growing transversally and leaving the lumen of the artery by penetrating through the wall. To either side of the artery one can see a dense neuroma consisting of contorted nerve fibers from the escaped masses. In contrast to the effects of large holes discussed in the preceding paragraph, this porosity of the arterial wall, while permitting profuse dissipation of nerve fibers into the surroundings, does not seem to favor reciprocal inflow of fibrous tissue. Consequently, masses of nerve fibers which lie outside the immediately affected area, particularly those deeper in the interior of the nerve, regenerate as well as they otherwise do in intact arterial sleeves. This is illustrated in figure 6B. This figure shows a longitudinal section through the same nerve as figure 6A, slightly distal to the level of the former, traveling through the gap within the intact part of the artery. Here the fibers have remained confined within the tube and have regenerated in strictly parallel longitudinal orientation with no branching or confusion.

The great number of nerve fibers seen in and around an area of decomposition of the sleeve (fig. 6A) offers no correct gage of the actual loss of fibers as sources for refilling of the peripheral stump, for, firstly, their contorted course

in this area makes the same fibers appear several times in the same section, and, secondly, there is evidence of extensive branching, attributable to the wealth of obstructions to fiber growth in this region. Accordingly, the peripheral stumps of nerves with lateral eruption of fibers are not as badly depleted after regenera-

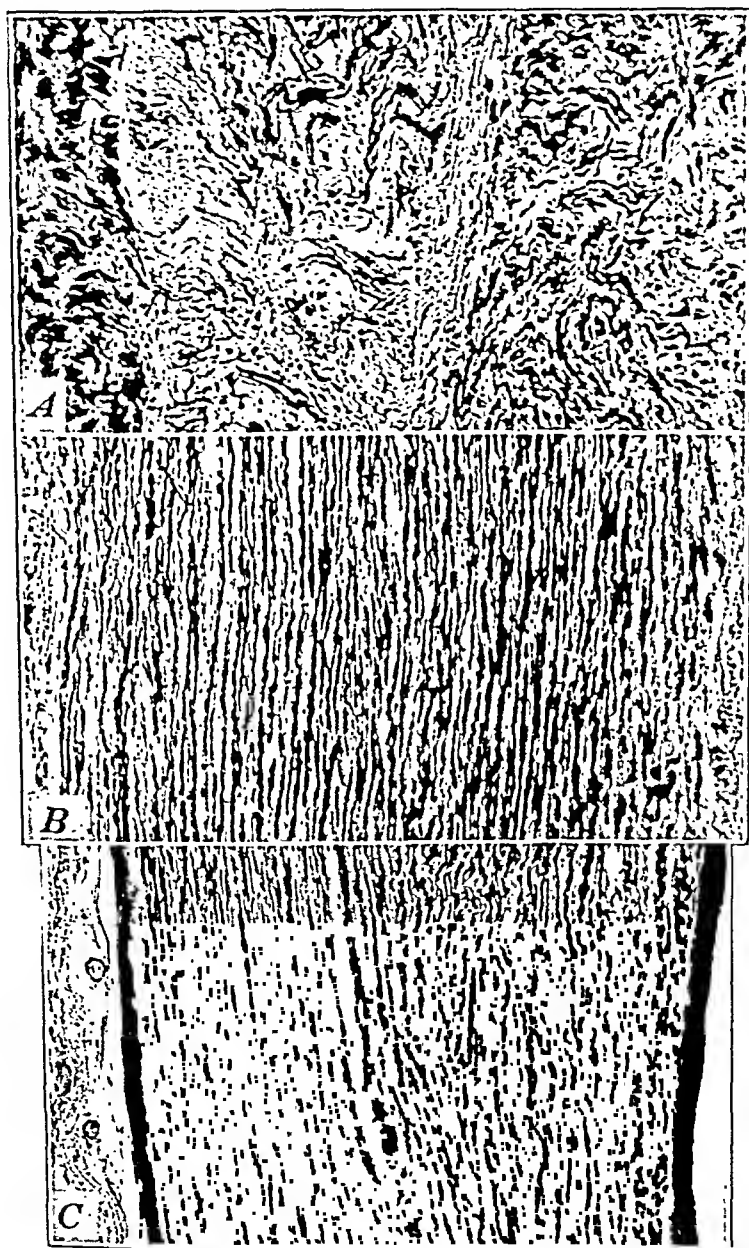


Fig. 6.—Effect of a local lesion in the arterial wall on growth of nerve fibers, one hundred and seventy days after operation. An explanation is found in the text ( $\times 112$ ).

tion as the size of these local neuromas would suggest. Figure 6 C shows a longitudinal section through the branching point between the peroneal and the tibial nerve (as in fig. 6 A and B). It shows the whole tract of the nerve filled

with regenerated fibers, and, while the total volume is slightly less than normal, it is not reduced nearly as much as one would have expected if the proximal fiber source had suffered a permanent reduction of such magnitude as figure 6 *B* would seem to indicate. Nevertheless, fiber counts on cross sections demonstrate that leaks in the artery wall do result in a certain permanent deficit of regenerated fibers in the peripheral stump. In one example, for instance, in which during the operation a lateral hole was made in the artery through which fibers later escaped, a fiber count proximal to the break of approximately 6,000 fibers dropped to approximately 2,200 fibers inside the nerve gap beyond the break, which figure rose only slightly farther distally to less than 2,600 fibers in the peripheral branches. Thus, while a negligible amount of regulative branching may have taken place, a definite deficit has remained.

Another type of failure results when a splice is made with arteries too small in diameter to accommodate the nerve without constriction. During the operation such arteries can, of course, be widened to the point where they can be forced over

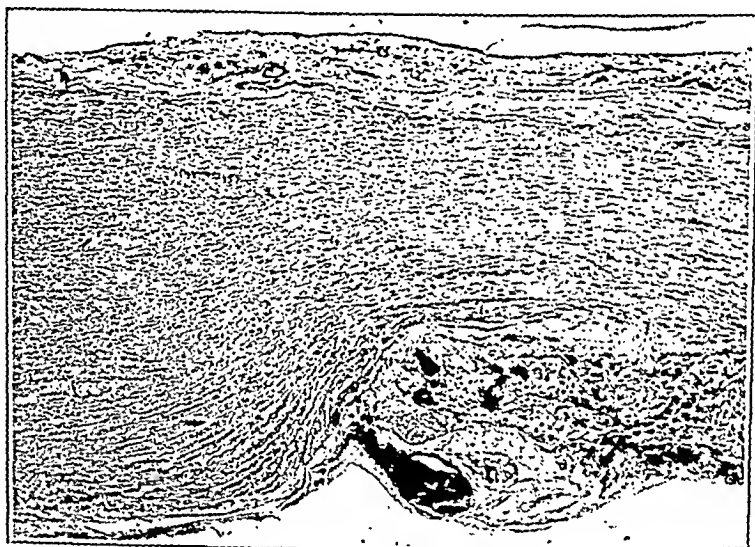


Fig. 7.—Compression of nerve fibers due to constriction of the sleeve; bottleneck at entry of the proximal stump into the sleeve, thirty-eight days after operation ( $\times 56$ ).

the nerve ends, but in postoperative stages they contract again and strangle the nerve in the interior. When this happens, the effects on the nerve are serious. The histologic appearance of such a regenerate is exemplified in figure 7, showing the proximal end of a constricted arterial sleeve. As one can readily see, the sleeve forms a bottleneck, inside of which the nerve fibers are condensed into a tightly packed bundle. Moreover, the proximal stump of the nerve is for some distance proximal to its entrance into the sleeve pathologic in appearance. A conspicuous edema is formed here, which gives the nerve a bulbous shape. The inside of the nerve is loosened up, fibers and fiber bundles are widely separated and retrograde degeneration has proceeded farther centrally than is found after mere nerve section. The edema proximal to the constriction is of great interest. It clearly demonstrates that there is normally in the nerve a centrifugal flow of "lymph." Obstructed by the tight packing of the fibers in the sleeve, this flow is arrested and the dammed-up fluid distends the nerve. A similar observation,

namely, an edematous condition of the nerve stump in constricted human nerves, has been reported by Dustin.<sup>16</sup>

Close inspection of the nerve fibers passing through the bottleneck reveals an abrupt change of their size and condition at the level of constriction. Proximal to this level there are many large fibers in advanced stages of maturation, while within the constricted area all fibers are small and immature, like those of very young regenerates. This does not mean that the large fibers have grown only as far as the level of the constriction and there become arrested, but rather that one and the same fiber has assumed large diameter in the proximal part but remained small and undeveloped within the compressed area. This could be ascribed to a sort of inanition effect resulting from the lymph stasis mentioned before, but it is more likely due to the obstruction of the centrifugal flow in the axis-cylinders themselves of some essential factor produced by the nerve cell body and required for continued growth in width of the peripheral fiber. This is suggested by the fact that the fibers just proximal to the level of constriction are often swollen and club shaped, as if some substance passing down the axon had become dammed up on the inside.<sup>17</sup>

The few such constrictions observed thus far were studied only five to six weeks after the operation. Therefore, it is impossible as yet to say whether the immaturity and small size of regenerated fibers under lateral compression are a permanent feature. However, in view of the tight packing of the fibers and the apparently firm stranglehold of the artery, it may be considered doubtful whether these fibers will ever have an opportunity of acquiring larger caliber. Some of these compressed nerves have been studied oscillographically and will be discussed on a later occasion. It may suffice here to say that this condition seems to set up a definite pressure block interfering with conduction along those fibers. Therefore, although complete neurotization of the peripheral stump may be obtained even under these conditions, the functional results of such regeneration are rather inadequate.

It is evident, then, that most failures of the arterial splice are due to improper manipulation during the operation or to the selection of arteries which are either too big, and thus admit extraneous fibrous tissue, or too small, and thus choke the nerve.

#### COMMENT

Properly executed, the arterial splice leads to a satisfactory reunion between proximal and peripheral stump and creates most favorable conditions for subsequent nerve regeneration, provided the two cut surfaces can be brought within fair proximity. It can be applied wherever there is enough slack on the nerve to permit apposition of the cut surfaces. However, intimate contact between the two ends is neither necessary nor desirable. Pressing the two ends together so as to produce flanging forces the nerve fibers into a tangle which a good suture tends to avoid. Moreover, it must be borne in mind that regeneration of the fibers does not actually start from the level of apposition but begins slightly more proximally, since a variable and uncontrollable amount of retrograde degeneration is bound to precede the onset of regeneration.

It has already been pointed out by Nageotte<sup>5</sup> that a slight gap between the nerve stumps is advantageous for regeneration, and the same general conclusion

16. Dustin, A. P.: Les lésions posttraumatiques des nerfs: contribution à l'histopathologie du système nerveux périphérique chez l'homme. *Ambulance de "l'Océan,"* 1917, vol. 1, pt. 2, pp. 71-161.

17. Parker, G. H.: On the Trophic Impulse So-Called: Its Rate and Nature, *Am. Naturalist* 66:147-158, 1932.



must be drawn from the present experiments. The size of the gap in our experiments can be reconstructed from longitudinal sections as the distance between the margins of the proximal and the distal epineurium. The epineurium, at least under the conditions of our experiments, has shown little tendency to regenerate, and its edges, therefore, mark the limits of the old nerve stumps rather distinctly. If these landmarks are used and allowance is made for the fact that they may have been slightly retracted during the healing process, it becomes evident that a gap up to 3 mm. between the original nerve ends is compatible with good nerve regeneration. Through such a gap regeneration takes place with the same strict orientation, fiber alinement and ease as if the fibers were proceeding inside a degenerated peripheral stump. Larger gaps have not been found equally passable, primarily for the reason that the arteries in such regions, lacking a solid core, tend to collapse so that their lumen becomes partly obstructed.

The question now arises as to what forms the matrix, i. e., the medium in which the nerve fibers grow while traversing the gap. Obviously the gap is no void but is filled with substance even before the regenerating nerve fibers arrive, and the composition and properties of this substance become a matter of great interest in that they seem to be exquisitely favorable for nerve growth. Save for the few instances with postoperative intraneural bleeding, no large blood clot was present between the stumps, and therefore the matrix of the gap does not consist of blood plasma. The tight fit of the arterial sleeve and its sealing to the nerve by rapid clotting prevent the seeping in of extraneous fluid. This seems to leave the interior of the nerve as the sole source of whatever medium fills the gap. It may be assumed to be primarily composed of an exudate of intraneural "lymph," possibly carrying additional products exuded from the severed nerve fibers and sheath cells. The connective tissue cells in the nerve do not seem to be numerous enough to be credited with a sizable contribution. That this nerve exudate is a reality has recently been demonstrated in tissue culture experiments in which embryonic ganglions and nerves were reared at the phase boundary between a cover slip and a liquid medium. It was noted that if the medium consisted of Tyrode's solution with or without a trace of blood serum added a film of substance would seep out from the living tissue along the phase boundary and that outgrowing nerve fibers would tend to hold themselves within that film. On fixation and impregnation with silver salts, the film reveals a fine reticulated structure, which would suggest that it contains fiber proteins or other fiber-forming elements capable of oriented aggregation. While much of this work is still in the exploratory stage, it definitely points in the same direction as the splicing experiments, namely, that nerve tissue when injured produces an exudate capable of becoming oriented and obviously most favorable, in biophysical and biochemical regards, for rapid nerve growth.

The role of the colloidal matrix in which nerve growth takes place has been discussed in earlier papers.<sup>18</sup> The orientation of nerve growth has been resolved essentially into a matter of the orientation of the surrounding colloidal particles plus the tendency of the growing nerve fiber to comply with this orientation of its surroundings. The exudate which accumulates between the nerve stumps is evidently capable of assuming such orientation and thereby serving as an oriented guiding substratum for the outgrowing nerve fibers. In this respect it seems not to differ significantly from fibrin clots, which were used in the earlier experiments on

18. Weiss.<sup>15</sup> Harrison, R. G.: The Croonian Lecture on the Origin and Development of the Nervous System Studied by the Methods of Experimental Embryology, *Proc. Roy. Soc., London*, s.B 118:155-196, 1935.

nerve fiber orientation and more recently by Young with good success for the union of severed nerve stumps. However, the tendency of the fibrin clot to become converted into dense connective tissue, with all the disadvantages such fibrosis entails for nerve growth, is absent in the exudate of nervous origin. Comparative studies are under way to determine whether the difference between a fibrin filling and a neural exudate in the lumen of the arterial splice is sufficiently pronounced to have practical significance.

I have said the matrix inside the sleeve is capable of becoming oriented, that is, it is presumably composed of rod-shaped polar ultramicros. To orient these, an orienting factor is required. This factor is provided by the longitudinal tension to which the nerve is subjected. The effect of such tension on a potentially fiber-forming matrix has been described earlier.<sup>19</sup> It forces the ultramicroscopic fibrillar units into parallel alinement. This has two consequences: First, it compels cells of the spindle type, i. e., fibrocytes as well as sheath cells, to extend in a similar direction, and, secondly, it orients the growth of the nerve tips accordingly. In regeneration this has the effect of presenting the nerve fibers with a system of guide rails along which the outgrowing sprouts can continue in a direct straight course, passing on without obstruction into the open tubes of the peripheral stump. At the same time this longitudinal organization prevents the formation of oblique or transverse patterns which would deflect the nerve fibers from their straight course and, in addition, cause profuse branching.

Nageotte<sup>2</sup> has asserted that growth of sheath cells from the peripheral stump centrad precedes the outgrowth of the nerve fibers. I have made no study of the early stages of regeneration in my experiments to test this point. If it should prove correct, the orientation of the gap region would have its primary effect on the hyperplastic sheath cells in that it would force them into straight line connections between the proximal and distal stumps, which then, in turn, would serve as invasion routes for the outgrowing nerve sprouts. It is likely that the orientation of the matrix straightens nerve growth both indirectly, by way of the sheath cells, and directly, by orienting nerve fibers advancing freely. At any rate, the unconfused and strictly oriented pattern of the regenerating fibers must be ascribed in last analysis to the tension in longitudinal direction which the nerve exerts on the matrix that seals its two ends.

It may be pointed out that most suture methods in which the two stumps are united by rigid threads fail to accord the area of regeneration the benefit of this longitudinal strain. Longitudinal stresses arising in nerves held together by silk sutures are taken up by the rigidity of the suture material or at best by the rather unelastic epineurium. This leaves the interior between the ends of the suture slack, and the region which needs longitudinal strain most for a good orientation of nerve growth has the least of it. The plasma suture of Young and his co-workers is the only other method in which the gap region is accorded the full advantage of longitudinal stress in the nerve. However, since such tension, while highly desirable for regeneration, is undesirable during the early stages of suture in that it may rupture the fresh union, the fibrin method has its well recognized limitations. The arterial splice, on the other hand, in providing a firm seal between the arterial segment and the two nerve stumps, yet being elastic enough to withstand considerable extension, reduces the danger of rupture while allowing full play to the orienting action of longitudinal strain.

19. Weiss, P.: Functional Adaptation and the Role of Ground Substances in Development. *Am. Naturalist* 67:322-340, 1933; footnote 15 b.

It must be kept in mind that the favorable results thus far obtained with this method have been proved valid only within the limits within which they have been tested, namely, for the nerves of the rat, which are comparatively small. How the method will work out with larger nerves and in higher mammals, including man, is a question that cannot be answered until the results of an extensive series of experiments being carried out at the present time have become known. But it is obvious that even if the method should fail on large nerves, it is still uniquely suited for the mending of small nerves which defy ordinary suture methods on account of their small caliber.

For reasons already mentioned the method is not indicated for reunion of severed nerves in cases in which either loss of substance or considerable retraction of the stumps has created a sizable gap. To repeat, the arterial sleeve does not serve as a conduit for nerve fibers over appreciable distances, although it does help to bridge small gaps, of a few millimeters, or, in terms of the size of the nerve, a length not exceeding the diameter. In the case of larger gaps, nerve grafts will have to be used as heretofore. Again, however, the union between the graft and the two nerve stumps is to be effected with the aid of arterial splices, one such splice uniting the proximal end of the graft to the proximal stump and the other the peripheral stump to the distal end of the graft. The longitudinal stress on the nerve tends to prevent the formation of a glial scar, fibrous ingrowth and constriction at the distal suture line, so that by the time the regenerating nerve fibers have reached this level they should find a smooth and well organized pathway for transit into the peripheral stump, instead of the impassable fibrous bulkhead often encountered at the distal suture line. Experiments to demonstrate this point are under way.

A point of great practical significance is the choice of the artery. The importance of correct caliber has been previously discussed. Another feature to be considered is the amount of musculature in the arterial wall. What is really needed for a successful splice is merely the tough and impenetrable layers of elastic tissue. It is to these that the artery owes the properties that make it so suitable for the purpose. The muscular tissue, if anything, is harmful. While no detailed study has yet been made of this point, it seems that the circular musculature of the artery may receive reinnervation from autonomic fibers in the region of the wound and resume contractions. Even without such innervation a spasm of the muscular wall could develop which would strangle the nerve in the arterial lumen. As a matter of fact, the constrictions described as causes of failure were probably in part due to a secondary reduction of the arterial lumen by the contraction of the muscular coat. Pending a more systematic investigation of the subject, it may be said, therefore, that an artery will be the better suited for the purpose of splicing nerves the smaller the amount of muscular tissue in proportion to the volume of elastic tissue present.

Veins do not seem to be the equal of arteries as splicing agents. Their wall easily becomes porous and pervious, with all the detrimental consequences to nerve regeneration discussed for accidentally perforated arteries.

Experiments exploring the possibility of using arteries stored in various ways are under way. The use of arteries fixed by ordinary histologic means, as with alcohol or solution of formaldehyde, is contraindicated. Such preserved arteries have been used repeatedly in the past for the purpose of "tubulating" nerve regeneration, but the loss of elasticity caused by the treatment makes such tubular fragments wholly unsuitable for the purpose of splicing. Means by which arteries can

be stored under sterile conditions for long times without losing either their elastic properties or their laminated texture, both of which are prerequisites for successful splicing, will be reported on a later occasion.

#### SUMMARY

A method is reported by which severed nerve stumps can be united without the use of sutures. It consists in sealing the nerve ends into a common tightly fitting sleeve of live artery. Histologic evidence is presented, based on experiments on rats, showing that when this method is used (1) a firm tie between the stumps is obtained which has adequate tensile strength and offers most favorable conditions to nerve fiber regeneration; (2) nerve fibers regenerate in straight parallel courses; (3) regenerating fibers do not branch, nor do they stray about, intermingle, escape from the nerve or form local neuromas; (4) regenerating fibers essentially retain their mutual topographic relations; (5) ingrowth into the nerve of fibrous connective tissue and strangling of nerve fibers by fibrosis are prevented; (6) no fibrous scars form at the suture lines, and (7) even the smallest nerves can be mended.

## ROLE OF TOXIN AND USE OF ANTITOXIN IN SYSTEMIC STAPHYLOCOCCIC INFECTIONS

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Since it is now recognized that some strains of staphylococci produce a potent exotoxin, it is important to correlate experimental studies of staphylococcus toxin with clinical observations on systemic staphylococcic infections which have been previously reported. The exotoxin is capable of producing several well defined effects on different tissue cells, but it has never been adequately demonstrated whether these effects are due to several different tissue-specific toxins or whether a single toxin affects each tissue differently. Nevertheless, the outstanding results of the action of staphylococcus exotoxin are: hemolysis of red blood cells (hemolysin), destruction of leukocytes (leukocidin), necrosis of skin and subcutaneous tissues on direct injection (dermonecrotoxin), rapid death of laboratory animals on intravenous injection (lethal factor), necrosis of certain other tissues, such as the renal glomeruli and the mucous membranes of the gastrointestinal tract, and irritation of the synovial membrane on injection into joints.<sup>1</sup>

*Effect of Toxin in Vivo on Laboratory Animals.*—Following the intravenous injection of a lethal dose of a potent staphylococcus toxin, free from staphylococci, into laboratory animals, a characteristic chain of events has been repeatedly observed.<sup>2a</sup> Within a few minutes after the injection the animal becomes weak or the hindlegs are paralyzed; the respirations become shallow and irregular, and the animal weakens to such an extent that it can no longer stand erect and rolls onto its side. Before death the animal has violent convulsions and the legs execute strenuous running movements. At death the animal goes into opisthotonos, and terminally expels urine or feces or both. Accompanying these symptoms in rabbits Joyner and his associates<sup>2</sup> have observed a marked increase of young myeloid cells in the bone marrow and proportionately in the circulating blood.

These symptomatic effects are associated with a severe cardiovascular response. Electrocardiographic changes indicating myocardial damage have been observed in laboratory animals by Nélis, Bouckaert and Picard<sup>3</sup> and by Dingle, Hoff, Nahum and Carey.<sup>4</sup> We have been able to confirm these changes in rabbits, and accompanying them we have seen a characteristic pattern of variations in the pulse rate.<sup>5</sup> Immediately after the intravenous injection of toxin the pulse rate under-

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1. (a) Blair, J. E.: The Pathogenic Staphylococci, Bact. Rev. **3**:97 (June) 1939. (b) Rigdon, R. H.: Staphylococcus Toxin: A Résumé, Am. J. M. Sc. **199**:412 (March) 1940.

2. (a) Joyner, A. L.: Personal communication to the author. (b) Joyner, A. L.; Rigdon, R. H., and Hare, R.: A Study of the Effects of Staphylococcus Exotoxin on Leucocytes and Bone Marrow of Rabbits, J. Bact. **33**:47 (Jan.) 1937.

3. Nélis, P.; Bouckaert, J. J., and Picard, E.: Contribution à l'étude de la toxine staphylococcique, Ann. Inst. Pasteur **52**:597 (June) 1934.

4. Dingle, J. H.; Hoff, E. H.; Nahum, L. H., and Carey, B. W., Jr.: The Effect of Staphylococcus Aureus Exotoxin on the Rabbit Heart, J. Pharmacol. & Exper. Therap. **61**:121 (Oct.) 1937.

5. Kleiger, B.; Blair, J. E., and Hallman, F. A.: Behavior of Rabbits After Infection with Toxicogenic and Nontoxicogenic Staphylococci: An Experimental Study, Arch. Surg. **45**:571 (Oct.) 1942.

goes a transient depression: this is soon followed by an increase in rate to about 50 to 100 beats per minute above the normal. As the summit of the increase is reached the pulse rate drops sharply, and with this the electrocardiographic changes previously mentioned appear.

*Toxin Production in Vivo in Laboratory Animals.*—Toxigenic staphylococci will produce exotoxin in vivo in laboratory animals, and the disease caused by the intravenous injection of these organisms in rabbits is different from the disease produced by nontoxigenic staphylococci similarly injected.<sup>5</sup> About twenty hours after the injection of a saline suspension of a culture of a toxigenic strain of staphylococci that had been thoroughly washed to remove any traces of free toxin there began the same characteristic chain of events that had been observed, in more rapid sequence, in animals which had received injections of toxin alone. The animals died within twenty-four hours in convulsions and in opisthotonos. The changes in the electrocardiogram and in the pulse rate were the same as those following the injection of toxin.

The reaction of rabbits to the intravenous injection of a saline suspension of a washed culture of nontoxigenic staphylococci was different from the reaction of animals which received toxigenic staphylococci. These rabbits also died within twenty-four hours. However, after about twelve hours they became lethargic, and then became progressively weaker until at some time between twelve and twenty-four hours they died quietly. At no time did they have violent convulsions, nor did they go into terminal opisthotonos. There were no electrocardiographic changes, nor was there any characteristic pattern of variation in the pulse rate.

Variations in immunity alter the response of an animal to infection by toxigenic staphylococci. In 1 animal so infected none of the characteristic symptoms of toxicity occurred; numerous abscesses developed, the rabbit's condition gradually deteriorated and after several days it died. None of the characteristic changes in the electrocardiogram or in the pulse rate developed. This picture was duplicated by administering adequate amounts of staphylococcus antitoxin to rabbits infected with toxigenic staphylococci.

*Effect of Toxin in Human Beings.*—The clinical importance of staphylococcus toxin first attracted wide attention after the disaster at Bundaberg, Australia, in 1928.<sup>6</sup> Twenty-one children were given a prophylactic dose of diphtheria toxin-antitoxin, and within thirty-six hours 12 of the 21 succumbed to a fulminating systemic disease characterized by diarrhea and rectal incontinence, a high fever and a rapid pulse rate out of proportion even to the elevated temperature. The patients rapidly went into coma, soon became completely irrational and died in delirium. In the children who survived abscesses developed later at the site of injection. From the abscesses was cultured the same strongly toxigenic hemolytic *Staphylococcus aureus* that was cultured from the single bottle of toxin-antitoxin which had been used for all the children.

Since such close resemblance exists between the symptoms of animals dying of the effects of staphylococcus toxin and the symptoms of the children who died in the Bundaberg disaster, it appears that in persons who are susceptible to the toxin infection by toxigenic staphylococci causes a chain of symptoms which are peculiar to the toxin. This has been demonstrated in a previously reported study.<sup>7</sup>

6. Kellaway, C. H.; MacCallum, P., and Tebbutt, A. H.: Report of the Royal Commission of Enquiry into the Fatalities at Bundaberg, M. J. Australia 2:2 (July 7); 38 (July 14) 1928. Foreign Letters (Australia), J. A. M. A. 91:262 (July 28) 1928.

7. Kleiger, B., and Blair, J. E.: Correlation Between Clinical and Experimental Findings in Cases Showing Invasion of the Blood Stream by Staphylococci, Surg., Gynec. & Obst. 71:770 (Dec.) 1940. Kleiger, B.: Granulocytopenia Following Acute Staphylococcal Osteomyelitis, Bull. Hosp. Joint Dis. 2:180 (Oct.) 1941.

in which we concluded that it is possible to determine from the clinical characteristics alone whether the symptoms are manifestations of disease due to the staphylococcus toxin or to other factors in staphylococcic infection. The onset of true staphylococcic toxemia in human beings is rapid, and the initial manifestations are systemic rather than local. The most frequent of these are abdominal pain, diarrhea, incontinence of feces or urine or both, meningismus, coma and delirium. These symptoms are acute during the first four or five days of illness, and the sooner they reach their maximum acuity the more pronounced has been the effect of the toxin on the patient. The pulse rate rises rapidly to a height out of proportion to the height of the temperature. In the most toxic patients the rate stays above 140 beats per minute. The importance of a low white blood cell count with a relative increase in the number of nonsegmented cells has been stressed as an index of toxicity.<sup>8</sup> We have found this to be of value as confirmatory evidence, but we depend to a greater degree on the clinical picture.

We have never found this picture in patients over 30 years of age, and therefore we have come to feel that such persons are more resistant to the systemic effects of the toxin. Thus, in older persons the disease develops more slowly and at first the symptoms are those arising from the local infectious lesion. To these are added later the symptoms of the disturbed metabolic processes associated with long-standing illness. The temperature may be greatly elevated, but in spite of this the pulse rate will not exceed 120 beats per minute early in the disease; however, circulatory embarrassment may occur later, and then the pulse rate will rise above 140 beats per minute. The prognosis in this group of patients usually depends on the health of the individual prior to his infection and on the site of local or metastatic lesions. Death results only when predisposing or intercurrent illness so weakens the patient that he is unable to withstand the onslaught of the infection, or when the infection attacks some vital organ or a region that cannot be satisfactorily drained surgically.

*The Therapeutic Use of Antitoxin.*—Since toxin plays an important role in certain staphylococcic infections, a potent specific antitoxin should be of therapeutic value.<sup>9</sup> Antitoxin cannot be employed indiscriminately for all types of staphylococcic infection, particularly those which are chronic or refractory to other forms of therapy; its use must necessarily be confined to those acute conditions in which the effects of toxin are clinically apparent.<sup>10</sup> The dosage should be adjusted to the degree of toxicity as well as to the size of the patient, somewhere between 1,000 and 2,000 units of antitoxin per pound (between 2,200 and 4,400 units per kilogram) of body weight being required for the first day. This dose is then reduced each succeeding day to just the amount necessary to control the patient's symptoms. It should not be necessary to continue the administration of antitoxin beyond the

8. (a) Baker, L. D., and Shands, A. R., Jr.: Acute Osteomyelitis with Staphylococcemia: Clinical Report on the Use of Antitoxin in Its Treatment, *J. A. M. A.* **113**:2119 (Dec. 9) 1939. (b) Baker, L. D.: Acute Osteomyelitis with Staphylococcus Septicemia, *South. M. J.* **34**:619 (June) 1941. (c) Joyner, A. L., and Smith, D. T.: Acute Staphylococcus Osteomyelitis: The Use of Staphylococcus Antitoxin as Aid to Management of Toxemia and Staphylococcemia, *Surg., Gynec. & Obst.* **63**:1 (July) 1936. (d) Joyner,<sup>2a</sup> (e) Joyner, Rigdon and Hare.<sup>2b</sup>

9. Dolman, C. E.: Staphylococcus Antitoxic Serum in the Treatment of Acute Staphylococcal Infections and Toxaemias, *Canad. M. A. J.* **30**:601 (June) 1934; **31**:1 (July); 130 (Aug.) 1934.

10. (a) Stookey, P. F., and Scarpellino, L. A.: Staphylococcus Septicemia, *South. M. J.* **32**:173 (Feb.) 1939. (b) Baker and Shands,<sup>8a</sup> (c) Baker,<sup>8b</sup> (d) Dolman,<sup>9</sup> (e) Joyner and Smith.<sup>8c</sup>

fourteenth day of the patient's illness, by which time the blood should contain a sufficiently high antitoxin titer.<sup>11</sup>

As with any type of serum therapy, the potential dangers of serum reactions always exist.<sup>12</sup> These reactions may be immediate or delayed. The most common and the least serious immediate reaction is thermal. Shortly after the injection of serum the patient feels chilly or undergoes a definite shaking chill; this is followed by a sharp rise in temperature, and may be accompanied by an increased pulse and respiratory rate and a varying degree of circulatory and respiratory collapse. The other immediate reactions are less frequent, but more serious. True anaphylaxis is always alarming and is often fatal. The symptoms are usually those accompanying rapid paralysis of the respiratory and circulatory centers. Another serious immediate reaction is the occasional occurrence of peripheral circulatory failure following the injection of serum. This usually occurs in persons with previously existing cardiovascular disease. The delayed serum reaction is the common serum sickness which appears seven to ten days after injection, and is characterized by urticaria, arthralgia and malaise. This form is readily controlled and requires little discussion.

For the administration of staphylococcic antitoxin we have adopted the following routine, which has been eminently successful. We first inject 0.1 cc. of undiluted antitoxin intracutaneously into the flexor surface of the forearm. Fifteen minutes later, if no reaction has occurred in the form of a wheal or formation of pseudopods surrounding the site of the injection, 2 or 3 cc. is injected intramuscularly into the buttock. Two hours later an intravenous infusion of 5 per cent dextrose in physiologic solution of sodium chloride is started. To the infusion fluid is added sufficient antitoxin to make a dilution of about 1:15. The serum is dispensed in vials each containing 20,000 units of antitoxin. It has been our practice to compute the total dose required for each day, and then to give 20,000 units at regular intervals until the required amount for that day has been administered. If the patient reacts positively to the cutaneous test, he is desensitized by the intramuscular injection, at intervals of one-half hour, of 2 cc., 3 cc., 5 cc. and 10 cc. of antitoxin. Desensitization is followed by the administration of antitoxin by the intravenous method just described, which is started about one to two hours after the last desensitizing dose. When serum preparations are being administered, epinephrine or ephedrine should always be available for immediate use.

Staphylococcus antitoxin when used in patients whose symptoms were actually due to toxin has brought about a most gratifying clinical improvement. Within twelve hours from the onset of therapy children whose symptoms had been fulminating became quiet and rational. Diarrhea and fecal and urinary incontinence

11. (a) Stookey, P. F.; Scarpellino, L. A., and Weaver, J. B.: Immunology of Osteomyelitis, Arch. Surg. 32:494 (March) 1936. (b) Weiss, C.: A Study of Natural and Acquired Immunity to Staphylococcal Toxin in Monkeys, J. Immunol. 37:185 (Sept.) 1939; (c) Availability of Staphylococcal Antitoxin After Intramuscular Injection into Normal Monkeys and Man, Proc. Soc. Exper. Biol. & Med. 43:441 (March) 1940; (d) Serum Antistaphylococcal Titters During Antitoxic Therapy of Staphylococcal Infections, Am. J. Clin. Path. 11:329 (April) 1941. (e) Stookey and Scarpellino.<sup>10a</sup>

12. (a) Besredka, A., and Gloyne, S. R.: Anaphylaxis and Anti-Anaphylaxis, and Their Experimental Foundations, St. Louis, C. V. Mosby Company, 1919. (b) Mackenzie, G. M.: Serum Disease and Serum Accidents, in Cecil, R. L.: A Textbook of Medicine, ed. 3, Philadelphia, W. B. Saunders Company, 1934. (c) Rutstein, D. D.; Reed, E. A.; Langmuir, A. D., and Rogers, E. S.: Immediate Serum Reactions in Man: Classification and Analysis of Reactions to Intravenous Administration of Antipneumococcus Horse Serum in Cases of Pneumonia, Arch. Int. Med. 68:25 (July) 1941.



ceased, and the pulse rate was reduced to a level in proportion to the temperature. The white blood cell count later rose to 15,000 to 20,000, and the number of nonsegmented cells diminished. Antitoxin has no direct effect on the staphylococcus or on the infection, but the neutralization of toxin doubtless aids nonspecific antibodies in combating and localizing the infection.<sup>13</sup>

The results of antitoxin therapy have in a manner confirmed our previous observations that true staphylococcic toxemia is associated with a characteristic clinical picture. More specifically, the patients exhibiting the characteristics of a true toxemia responded rapidly and well to the administration of staphylococcic antitoxin. Conversely, patients above the age of 30 and others who did not show evidence of toxemia did not respond to antitoxin in this manner.

Our present therapeutic approach has been followed only since December 1939. Since then we have treated, without a single death, 4 children with definite toxic symptoms and bacteremia and 4 with mild to moderate toxicity and bacteremia. Three other children who were similarly treated also survived; 1 of these had obvious toxic symptoms and bacteremia, and 2 had moderately toxic symptoms, but their blood cultures remained sterile. These 3 patients are mentioned separately because of insufficient data for a complete study. A laboratory study of the staphylococci isolated from material obtained from 9 of the patients confirmed the correlation between the toxigenicity of the organism and the character of the clinical symptoms which we had previously observed. All of these patients were treated with what we considered to be adequate amounts of a commercial staphylococcus antitoxin.<sup>14</sup> Additional treatment in the form of transfusions, fluids and sedation was given as indicated. Sulfonamide compounds in the form of thiazole derivatives and sulfadiazine were given at some stage in the majority of the cases, but their value cannot be properly estimated. In no instance did a prompt remission follow the administration of a sulfonamide compound, and the course of the patients treated with sulfonamide compounds did not differ from that of the patients in whose cases the drugs were not used. On the basis of the clinical response we feel quite certain that the sulfonamide compounds have no clinical effect on the toxic phase of staphylococcic infections.

We can probably best illustrate the effectiveness of antitoxin by describing the response of 2 children with definitely toxic symptoms who received adequate amounts of the antitoxin without the concurrent use of sulfonamide compounds.

#### REPORT OF CASES

CASE 1.—A 7 year old boy, previously reported on by Dr. Carroll M. Silver before the Clinical Society of this hospital,<sup>14</sup> was admitted on the third day of illness with acute hematogenous osteomyelitis of the upper end of the tibia and staphylococcic bacteremia. His temperature was 105.2 F. and his pulse rate 155 beats per minute; he was comatose, completely irrational and incontinent of feces. Antitoxin was administered according to the technic described, with no serum reaction. Within twelve hours the boy received 120,000 units of antitoxin and by the end of that time he was mentally clear and alert and able to take fluids. By the next morning the pulse rate was 120 and the temperature was 100 F., and from then on recovery was uneventful. He was given 340,000 units of antitoxin in five days. Chart 1 shows the pulse and temperature records for the first fourteen days of hospitalization.

13. Mr. S. D. Beard of the Lederle Laboratories, Inc., made available a generous supply of Staphylococcus Antitoxin (Lederle) for this work.

14. Silver, C. M.: Staphylococcus Bacteremia with Osteomyelitis: Problems and Treatment, paper read at the meeting of the Clinical Society, Hospital for Joint Diseases, Oct. 7, 1941.

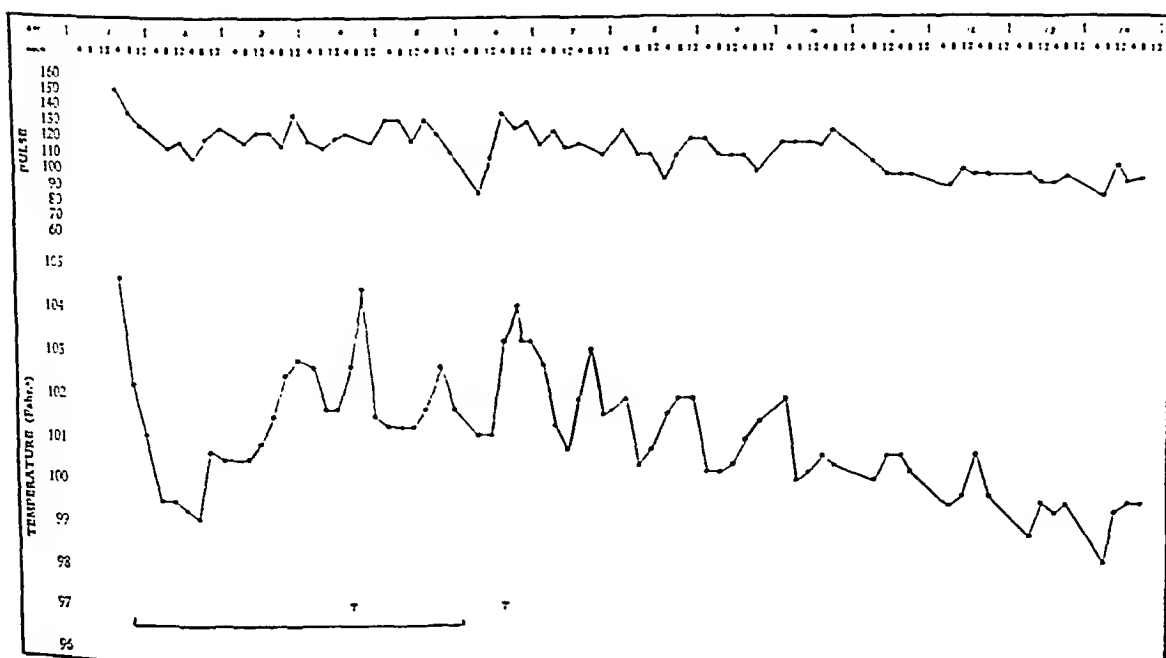


Fig. 1.—Pulse and temperature record in case 1. Antitoxin was administered over the period indicated by the solid line at the bottom of the chart. Blood transfusions are indicated by T.

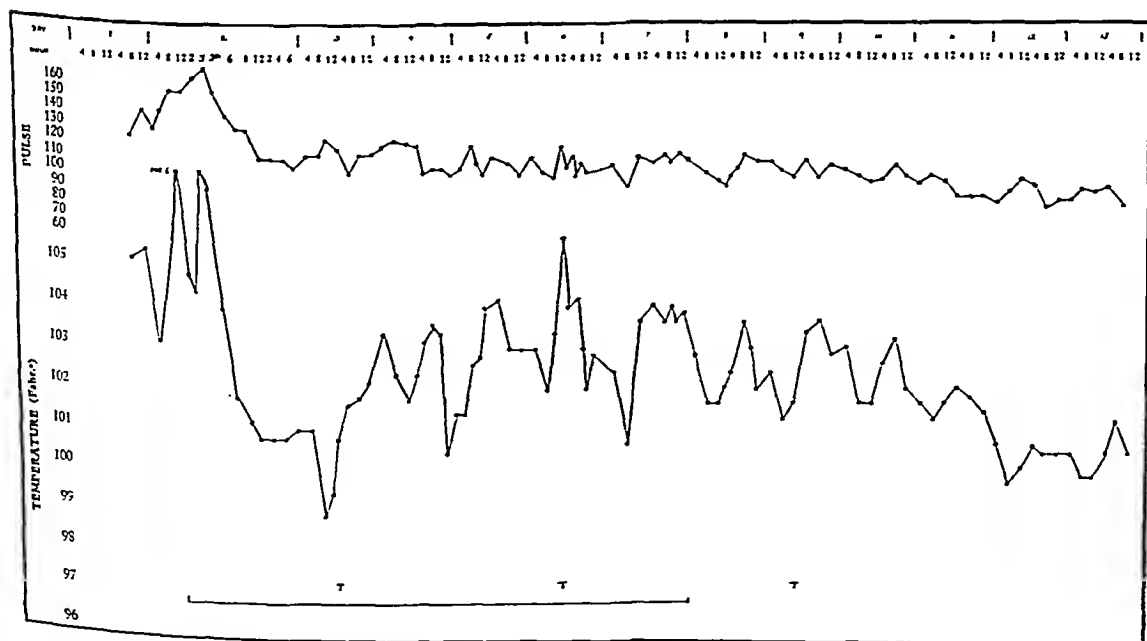


Fig. 2.—Pulse and temperature record in case 2. Antitoxin was administered over the period indicated by the solid line at the bottom of the chart. Blood transfusions are indicated by T.

CASE 2.—A girl of 9 years was admitted to the hospital after one day of illness with acute osteomyelitis of the upper end of the tibia and staphylococcal bacteremia. On her admission the temperature was 105.6 F., the pulse rate was 128 and she appeared to be only moderately toxic. By the next morning her temperature had risen to 108.6 F. and the pulse rate to 156, and she was completely irrational and unresponsive. Twenty thousand units of antitoxin was given by the recommended technic with no serum reaction. However, it was felt by the attending physicians that the serum should be administered more rapidly, and a second dose of 20,000 units was given undiluted by vein. This was followed by a severe thermal reaction, consisting of chills, convulsions and a one minute period of total apnea. Her temperature then rose again to 108.6 F., and the pulse rate to 168 beats per minute. She recovered from the reaction, and two hours later we resumed intravenous serum therapy by the proper technic. One hundred and forty thousand units was given on the first day, and within twelve hours her temperature was 101.2 F., the pulse rate was 118, and her symptoms were greatly improved. For two days she had periods of disorientation, but recovery proceeded. This child was given 480,000 units of antitoxin in six days. Chart 2 shows the pulse and temperature records for the first thirteen days of hospitalization.

Such results are in sharp contrast to those obtained in a comparable group of 14 patients under 30 years of age who were treated before December 1939, all of whom had toxic symptoms. Six were definitely toxic, and the organism cultured from the blood in each instance was a very potent toxin producer. These 6 patients all died within nine days of onset of the illness. Five others had mild to moderately toxic symptoms, but severe persistent infection was superimposed on these patients, who were already weakened by the toxin, and all 5 succumbed. Three children of the entire group survived. One had symptoms of moderate toxicity, and the offending staphylococcus produced a potent toxin. This patient received fair amounts of antitoxin and survived. The other 2 children had symptoms of mild toxicity, their infections were controlled and they survived. Many therapeutic modalities were employed for these 14 patients, the most frequent being bacteriophage, the then known sulfonamide compounds, and staphylococcus antitoxin. There were instances in which a temporary response to antitoxin occurred, but, in the light of our present knowledge, the serum was improperly given and in inadequate dosage, and we do not believe that death in these instances can properly be attributed to failure of the antitoxin. The other medications showed no promise at all.

#### SUMMARY

Certain strains of staphylococci will produce a potent exotoxin under special in vitro conditions.

This exotoxin when injected intravenously into experimental animals causes a characteristic response ending in the death of the animal.

Toxigenic staphylococci when injected intravenously into experimental animals are capable of producing exotoxin in vivo with the resultant characteristic response.

Systemic infection by toxigenic staphylococci in human beings who are susceptible to the toxin is associated with clinical symptoms which are characteristic and readily recognizable.

This exotoxin can be neutralized in vivo by commercial staphylococcus antitoxin, which produces dramatic and life-saving results when properly administered. The use of staphylococcus antitoxin in certain cases exhibiting the characteristic features of staphylococcal toxemia is recommended as a valuable adjunct in their therapeutic management.

The members of the attending staff and the house staff of the Hospital for Joint Diseases and Drs. Charles Wise and Henry M. Kaessler, of the Mount Vernon Hospital, Mount Vernon, N. Y., cooperated in the work reported in this article.

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# TRIGEMINAL NEURALGIA DUE TO RADICULAR LESIONS

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The partial section of the trigeminal sensory root by the temporal approach, as perfected by Spiller and Frazier from the Hartley-Krause operation for the relief of trigeminal neuralgia, has been acclaimed the most perfect operation known to surgery. A certain degree of morbidity indicates that this perfection is only relative. In search of a better treatment for this disease, Dandy<sup>1</sup> in 1925 began cutting the sensory root near the pons by the subcerebellar approach. While this operation has improved some morbidity rates, it has not eliminated them. Because the depth and location of the point of rhizotomy expose other nerve roots and important blood vessels to operative trauma, the majority of neurosurgeons have not discarded Frazier's operation in its favor.

One of the important by-products in the development of the suboccipital approach was the disclosure of a previously unrecognized frequency of gross etiologic lesions. In the first 200 cases in which this operation was used, Dandy<sup>2</sup> found that in 10 cases (5 per cent) a tumor of the cerebellopontile angle was responsible for the condition. In another series,<sup>3</sup> of 250 cases, he found 18 tumors of the cerebellopontile angle. In 1939<sup>4</sup> he stated that in 5 per cent of cases the pain is due to a tumor, in another 5 per cent of cases to an aneurysm of the basilar artery and "in nearly all others" to a vascular anomaly causing pressure on the sensory root. In 1941<sup>5</sup> he found "approximately 10 per cent" of cases of trigeminal neuralgia caused by a tumor in the cerebellopontile angle. Hyndman, who also employs the subcerebellar approach frequently, stated<sup>6</sup> that he had not yet found a tumor responsible for the pain, but<sup>7</sup> that if there exists the slightest doubt of the possibility of a tumor of the cerebellopontile angle, the cerebellar approach is the one of choice. He expressed the opinion that such a lesion should betray its presence by at least a diminution of the corneal reflex.

## THE LOCATION OF LESIONS PRODUCING TRIGEMINAL PAIN

Authors have expressed various opinions as to the cause and site of origin of the pain of trigeminal neuralgia. It is the general consensus that an organic lesion

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of the trigeminal pathways produces pain associated with sensory changes and not easily mistaken for major trigeminal neuralgia. The literature affords ample evidence that this is not always true and that a lesion affecting the trigeminal system in one of several places may produce pain indistinguishable from that of tic douloureux.

*Peripheral Branch of Nerve or Gasserian Ganglion.*—Dandy<sup>1</sup> stated that while pressure on the sensory root may produce trigeminal neuralgia, pressure on a peripheral branch of the nerve or the gasserian ganglion can never produce paroxysmal pain. This type of pain always means pressure on the root between the ganglion and the brain stem. Frazier<sup>8</sup> reported a case of a meningioma involving the dura over the ganglion, producing "jumpy" pain "like tic" but with a background of steady pain and with numbness of the lip. Cushing<sup>9</sup> said that while a tumor of the middle fossa compressing the gasserian ganglion may cause trigeminal pain, it usually is not like tic, being more continuous and accompanied by sensory loss. Peet<sup>10</sup> reported 2 cases of tumor of the antrum invading the maxillary nerve and ganglion, not affecting the sensory root. The patients had ticlike pain but with a background of pain, burning and numbness of the face. Mixer and Lund<sup>11</sup> reported a case of malignant neurogenic (?) tumor progressing along the maxillary nerve into the ganglion, also producing "lancinating pain" and sensory loss. On the other hand, Hyslop<sup>12</sup> reported a case of osteoma of the middle fossa compressing the first and second divisions of the trigeminal nerve near their foramina of exit. The patient had suffered tic for eighteen years and had received the usual relief from injection of alcohol. The pain was relieved by removal of the osteoma, the sensory root not being severed. Love and Woltman<sup>13</sup> reported 2 cases of tumor of the cavum Mecklii producing tic douloureux. One growth was an epidermoid among the posterior rootlets; the other, a meningioma beneath the root and ganglion. One patient was not entirely free of discomfort between paroxysms; otherwise the clinical picture in both cases was typical of trigeminal neuralgia. These were the only unsuspected tumors disclosed by rhizotomy for tic douloureux. I<sup>14</sup> have recently seen a patient whose sole complaint was typical tic in the distribution of the second division, caused by an aneurysm of the internal carotid artery within the cavernous sinus. The peripheral branch (maxillary) and possibly the ganglion were compressed by the lesion. Glaser<sup>15</sup> considered the ganglion the site of origin of tic pain. In general, while organic involvement of the ganglion and a peripheral branch of the nerve produces pain and sensory loss that are characteristic, the syndrome may not be complete and may pass for trigeminal neuralgia.

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14. Hamby, W. B.: Trigeminal Neuralgia Due to a Subclinoid Aneurysm of the Internal Carotid Artery, *Neurosurg. Ward Rounds* **3**:1 (Oct.) 1941.

15. Glaser, M. A.: Tumors Arising from Sensory Root of Trigeminal Nerve in Posterior Fossa: Perineurial Fibroblastoma, *Ann. Surg.* **101**:146-155 (Jan.) 1935.

*Sensory Root.*—In his monograph "Tumors of the Nervus Acusticus," Cushing<sup>16</sup> stated that these tumors produce neuralgic pain relatively infrequently and that none of his patients presented pain characteristic of tic douloureux. He mentioned a case of cholesteatoma reported by Krause,<sup>17</sup> a case of meningioma (?) reported by Lexer<sup>18</sup> and a case of sarcoma reported by Weisenburg,<sup>19</sup> in each of which the tumor had produced ticlike pain. He emphasized the point that paralytic rather than irritative trigeminal phenomena predominate with tumors of the cerebellopontile angle. Glaser,<sup>15</sup> in reporting a case of primary perineurial fibroblastoma of the trigeminal sensory root, found no ticlike pain and attributed its absence to the fact that the gasserian ganglion was not involved. Dandy<sup>20</sup> reported a case of tic due to a small acoustic neurinoma and said<sup>2</sup> that the tic so produced is clinically indistinguishable from that not due to a tumor. Parker<sup>21</sup> reported 2 cases of tic due to an acoustic tumor. In 5 cases of tic with gross etiologic lesions, Raney and Raney<sup>22</sup> found adhesions of the sensory root in the temporal region (cases 1 and 4) and compression of the root in the cerebellopontile angle by varices (case 2) and acoustic neurinomas (cases 3 and 5). In Weisenburg's case<sup>19</sup> both trigeminal and glossopharyngeal neuralgia were produced by a "sarcoma" of the cerebellopontile angle.

*Central Sensory Pathways.*—In a discussion of trigeminal neuralgia accompanying multiple sclerosis, Finesilver<sup>23</sup> stated that he was unable to come to a conclusion as to the location of the lesion producing trigeminal pain. He mentioned 3 cases in which the pain was relieved by section of the root and injection of alcohol but could not explain the fact that it was relieved by maneuvers that were peripheral to its probable origin. Frazier, Lewy and Rowe<sup>24</sup> concluded that trigeminal neuralgia, and eventually other forms of typical neuralgia, represent special forms of the thalamic syndrome. In 1 case of typical thalamic pain, they relieved the facial pain by injection of alcohol into the trigeminal nerve and the pain in the body by cordotomy. This suggested to them that thalamic pain can be relieved by abolishing afferent impulses to the thalamus. In postmortem studies on patients who had had trigeminal neuralgia, Lewy and Grant<sup>25</sup> found degeneration of the internal and lateral thalamic nuclei bilaterally, with loss of white matter and widening of the ventricles. In 5 patients with unilateral lesions the softening was on the side of the pain. Lewy and Grant offered evidence that these lesions were caused by functional or organic vascular insufficiency.

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17. Krause, F.: Operationen in der hinteren Schädelgrube, *Arch. f. klin. Chir.* **81**:40-60, 1906.

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19. Weisenburg, T. H.: Cerebello-pontile Tumor Diagnosed for Six Years as Tic Douloureux: Symptoms of Irritation of the Ninth and Tenth Cranial Nerves, *J. A. M. A.* **54**:1600-1604 (May 14) 1910.

20. Dandy, W. E.: Operations for Cure of Tic Douloureux: Partial Section of Sensory Roots at Pons, *Arch. Surg.* **18**:687-734 (Feb.) 1929.

21. Parker, H. L.: Paroxysmal Trigeminal Pain with Tumors of the Nervus Acusticus, *J. Neurol. & Psychopath.* **17**:256-261 (Jan.) 1937.

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23. Finesilver, B.: Trigeminal Neuralgia in Multiple Sclerosis, *J. Nerv. & Ment. Dis.* **90**:757-764 (Dec.) 1939.

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## PERSONAL EXPERIENCES

Probably as the result of training, I prefer to use the temporal approach to the root in uncomplicated cases of tic douloureux. The cerebellar approach has been employed in only 9 cases in a series of 109 operations for trigeminal neuralgia, although it was used in an additional 10 cases in which some other sensory root was severed for relief of pain due to a malignant tumor. In 2 of the 9 cases, a "pearly tumor" (epidermoid) of the cerebellopontile angle was found. The cerebellar approach was chosen in 1 of the 9 cases because of minimal symptoms suggestive of such a tumor, in another because the pain followed (four and one-half years) the previous removal of a meningioma of the cerebellopontile angle and in 2 others because a previous unsuccessful temporal operation on the sensory root or a peripheral branch of the nerve had so distorted findings that the possibility of a tumor could not be excluded clinically.

## REPORT OF CASES

*CASE 1.—Patient of 31 years with typical third division tic douloureux of six months' duration, with occasional "dizziness"; injection of alcohol into third division of trigeminal nerve, followed by imperfect relief and by slight homolateral facial paresis; suboccipital approach to sensory root, dislosure and removal of epidermoid of cerebellopontile angle; relief.*

Mrs. M. D., aged 31, was referred by Dr. W. J. Tracy, of Hornell, N. Y., on Jan. 20, 1936. In July 1935 she had experienced her first attack of paroxysmal, instantaneous pain in the right side of the lower jaw radiating anterior to the ear. Talking and laughing initiated attacks, but no history of an external "trigger zone" was obtained. In November the attacks became more frequent and often followed one another closely. In December her teeth were extracted, but no relief resulted. She admitted occasional "dizziness," although no history of vertigo was obtained. The neurologic examination revealed no abnormalities. Alcohol was injected into the third division of the trigeminal nerve, producing anesthesia and relief of pain.

On Feb. 11, 1936, the patient was admitted to the Buffalo General Hospital. The paroxysmal attacks of pain had ceased, but the jaw still was "sore." At that time there was a question of very slight weakness in the lower part of the face on the right side. Because of the history of slight dizziness and the questionable facial paresis, it was decided to approach the root posteriorly through the cerebellopontile angle rather than through the temporal fossa.

On Feb. 12, 1936, this approach was made with the patient under anesthesia induced with avertin with amylene hydrate and in the sitting position (fig. 1). The seventh and eighth cranial nerves were found normal. Just anterior to them was seen the tip of a typical "pearly tumor" (epidermoid). Its very thin capsule was opened, and the flocculent content was removed. The mass extended anterior to and beneath the fifth nerve, which was displaced backward. Its size was estimated to be 12 by 24 mm., its long axis being in the sagittal plane. At the completion of the procedure the fifth nerve was free in its course and so was not severed. The usual closure was made.

A letter written on May 4, 1938 stated that the patient was free of symptoms.

*CASE 2.—Woman of 41 years with typical second and third division tic douloureux for four years; three injections of alcohol, each followed by relief for decreasing periods; temporal section of sensory root planned; on morning of operation, first attack of vertigo, tinnitus and emesis with nystagmus and diminished corneal reflex for first time; exploration of cerebellopontile angle; removal of epidermoid; partial section of sensory root; relief.*

Mrs. M. P., aged 41, was referred to the Buffalo General Hospital by Dr. Robert Tuttle, of Gowanda, N. Y., on Dec. 26, 1940. For four years she had suffered attacks of typical trigeminal neuralgia in the areas of distribution of the second and third divisions of the left fifth nerve. Two years before, alcohol had been injected by a dentist into the third division. There was relief of pain for twenty-one months. A second injection gave relief for four months, and a third, no relief at all.

The neurologic examination gave entirely normal results except for revealing typical "trigger zones" in the upper and lower lips. The patient was scheduled for temporal sensory rhizotomy on the following day.

On the morning of operation, she awakened feeling dizzy, complained of tinnitus on the left side and vomited. Examination revealed nystagmus on looking to either side and diminution of the left corneal reflex. The remainder of the neurologic examination gave negative results. Because of this series of events, it was decided to explore the cerebellopontile angle and to do a partial rhizotomy if no lesion was found.

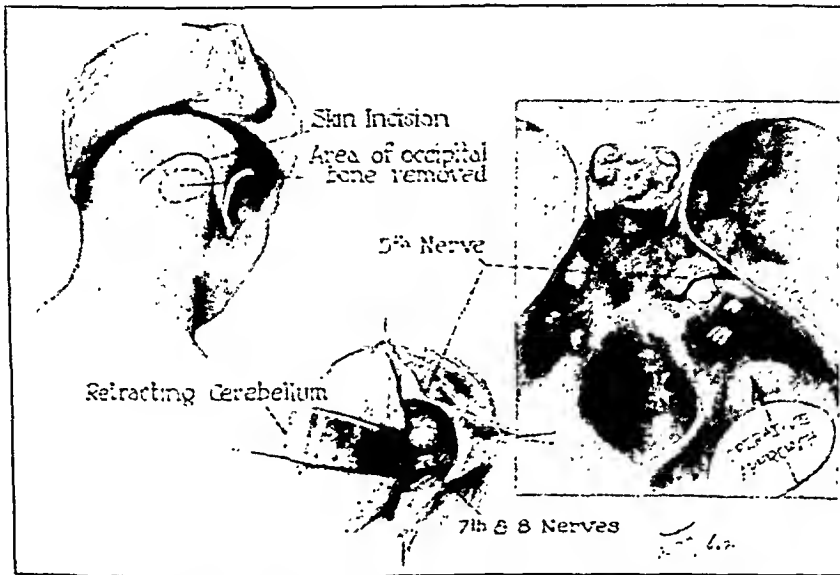


Fig. 1 (case 1).—Small epidermoid ("pearly tumor") under sensory root of trigeminal nerve, producing tic douloureux.

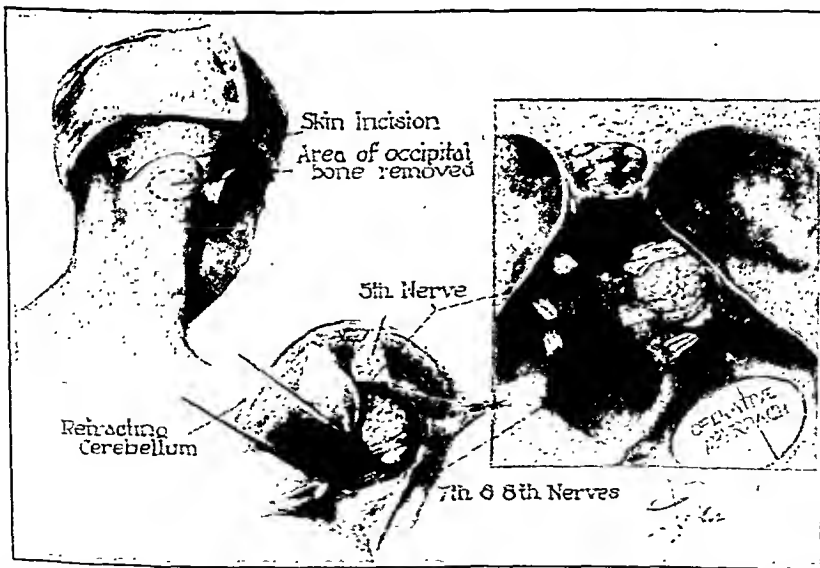


Fig. 2 (case 2).—Epidermoid ("pearly tumor") under sensory root of trigeminal nerve and facial and acoustic nerves, producing tic douloureux.

On December 27, with the patient under anesthesia induced with pentothal sodium (given intravenously) and in the sitting position, the left cerebellopontile angle was explored (fig. 2). At the level of the jugular foramen, a typical "pearly tumor" (epidermoid) 8 mm. in diameter was exposed. This was removed, and as its anterior end was reached it was found to be



attached to a much larger mass in the cerebellopontile angle. It was lobulated, and most of it lay behind the seventh and eighth nerves but a rather large mass extended anterior to the fifth nerve. After the soft contents had been evacuated, the capsule was teased out as completely as possible. The fifth, seventh and eighth nerves had been elongated by traction. The lower half of the fifth nerve was cut to prevent recurrence of pain. The usual closure was made.

Postoperatively, analgesia was present in the domain of the second and third divisions of the fifth nerve and the mild paresis of the lower part of the face persisted. The patient was discharged on Jan. 8, 1941.

*CASE 3.—Woman of 60 years with syndrome of tumor of right cerebellopontile angle; removal of meningioma of internal acoustic meatus; relief, two years later, short period of tic douloureux on left side, which subsided; four and one-half years later, onset of tic on right side; findings suggested recurrence of neoplasm; exploration revealed only arachnoid adhesions involving trigeminal sensory root; partial section of root; relief.*

Mrs. A. V., aged 60, was seen in consultation with Dr. C. W. Streets, of Fort Erie, Ontario, Canada, on Feb. 14, 1935. She had suffered paroxysmal attacks of tinnitus on the right side for five years and had had gradual visual failure for one year. For one month she had noticed paroxysmal attacks of vertigo and vertex headaches. For ten days slight pain and numbness had affected an area about the right eye and the lower right front teeth and paresthesias had involved the right arm and hand.

Examination revealed opacity of both lenses and no papilledema. The corneal reflexes were intact. No nystagmus was found. Hypalgesia was present around the lateral end of the right supraorbital ridge and at the right angle of the mouth. No facial paresis was seen. Hearing by both air and bone conduction was diminished in the right ear. Caloric vestibular tests revealed a nonfunctioning right labyrinth. The extremities were not ataxic, but the patient fell forward on bending. Hyperesthesia was demonstrated on the dorsum of the right hand. A diagnosis of tumor of the right cerebellopontile angle was made.

The patient was admitted to the Buffalo General Hospital on Feb. 20, 1935. On the following day the right cerebellopontile angle was explored. The nerves entering the jugular foramen were normal. Growing from the internal acoustic meatus was a firm, friable, reddish gray ovoid tumor, 15 by 20 mm., extending upward and anteriorly. The capsule was collapsed by curettage of the contents, one large afferent artery being coagulated and severed. The seventh and eighth cranial nerves then were seen pushed forward by the mass and not grossly implicated in its growth. The tumor was adherent only to the dura at the posterior lip of the internal auditory meatus. The fifth nerve was seen farther forward and did not appear grossly involved. The capsule was excised cleanly, and its base was coagulated. The usual closure was made.

Pathologic examination revealed a typical meningioma. The patient's convalescence was complicated by an attack of cholelithiasis, from which she recovered. Except for deafness of the right ear the symptoms and signs referable to cranial nerves all subsided prior to her discharge, on March 13.

She returned on June 26, 1940. A cholecystectomy had been done three years before. In 1938 she had suffered for four months with typical attacks of tic douloureux on the left side, which had cleared completely. For the past eight months she had suffered typical attacks of tic on the right side. She felt somewhat dizzy, and since she was almost blind from progression of the cataracts, she could not walk well alone. Examination revealed opacity of both lenses that precluded inspection of the optic disks. Otherwise the eyes were normal. There was no paresis of facial motion or sensation. The right ear was deaf. The right side of the body was weaker than the left, and both hands were ataxic. The reflexes were hyperactive but were equal on the two sides. A recurrence of the neoplasm was suspected.

On June 30 the patient was readmitted to the Buffalo General Hospital, and on the following day the right cerebellopontile angle was again explored, by reopening the old incision. The seventh and eighth nerves were diminished in size, but there was no evidence of recurrence of the neoplasm. The sensory root of the fifth nerve was firmly ensheathed in arachnoid adhesions. This root was isolated, and the posterior two thirds was severed. The usual closure was made.

After the operation she was free of pain. The right side of the face was anesthetic except for the cornea, and there was some weakness of the left arm and leg that persisted until her discharge, on July 11.

CASE 4.<sup>26</sup>—Woman of 48 years, with syndrome of a right acoustic neurinoma; severe third division trigeminal neuralgia on right side five years before; four years before, subtotal resection of sensory root, with complete relief; operation followed by tinnitus on right side for eight months and progressive deafness of right ear; two years before recurrence of pain in distribution of second division of right trigeminal nerve; peripheral neurectomy and injection of alcohol ineffectual; removal of acoustic neurinoma.

Mrs. E. R. M., aged 48 years, was admitted to the Cleveland Clinic on Dec. 17, 1933. Five years before, she had suffered typical trigeminal neuralgia in the right side of the lower jaw. A year later a subtotal resection of the sensory root was done elsewhere. After the operation the patient noticed tinnitus and progressive deafness and pain in the right ear. Within eight months the deafness was complete and tinnitus ceased. Three years later, typical tic developed in the distribution of the second division of the right fifth nerve. Peripheral operations and injections resulted in painful anesthesia. For two years she had staggered occasionally in walking.

Examination revealed horizontal nystagmus on lateral gaze. The optic disks showed borderline edema. The visual fields were normal. Both corneal reflexes were absent. The skin of the face was anesthetic in the distribution of the third division of the right trigeminal nerve and was hyperesthetic painfully in the distribution of the second division. Taste was lost in the right half of the tongue. The jaw deviated to the right on opening. There was mild peripheral paresis of the right side of the face. The right ear was deaf, and the labyrinth did not respond to caloric stimulation. The tendon reflexes were exaggerated, without Babinski's sign. Romberg's sign was present mildly, and no other ataxia was found. A diagnosis of trigeminal neuralgia secondary to an acoustic tumor on the right side was made.

Intracapsular removal of an acoustic neurinoma was performed by Dr. Gardner on Dec. 18. The portion of the capsule that seemed to carry the seventh nerve was preserved. The fifth nerve could not be found and was believed to have been destroyed with the capsule. The patient recovered, and some sensation returned to the right side of the face.

#### COMMENT

In case 1 the findings suggestive of a tumor of the cerebellopontile angle were meager. The patient was 31 years old, younger than the average person suffering from trigeminal neuralgia, though Dandy<sup>2</sup> has reported the disease in a child of 15 and Klemme<sup>27</sup> in a boy of 10 years. Mild homolateral tinnitus and a mild facial weakness (which was apparent only after an injection of alcohol three weeks before) were the only other suggestive phenomena. In case 2 no suspicion of a neoplasm was entertained until on the morning of operation the patient complained of vertigo and displayed nystagmus and corneal hypesthesia for the first time since she had been under observation. Interestingly, both of these patients had obtained the usual amount of relief following injection of alcohol into the peripheral nerves. This phenomenon also was recorded by Abbott and Merkel.<sup>28</sup> Blocking afferent stimuli at times may relieve pain due to a lesion of the sensory root as well as that due to a central lesion, as suggested by Frazier.<sup>8</sup> Relief is not always obtained in this way. Weisenburg's<sup>19</sup> patient did not obtain relief after section of the sensory root; the pain may have been attributable to the glossopharyngeal involvement. In case 4 pain was relieved in the area denervated by section of the root but persisted in spite of peripheral operations in later affected areas.

26. The presentation of this case was made possible by Dr. W. James Gardner, of the Cleveland Clinic, Cleveland, Ohio. Brief reference has been made to it previously (Hamby, W. B.: Acoustic Neurinomas in the Stage of Normal Intracranial Pressure, New York State J. Med. 35:1143-1147 [Nov. 15] 1935.

27. Klemme, R. M.: Accurate Subtotal Resection of Sensory Root for Relief of Major Trigeminal Neuralgia, South. M. J. 28:1086-1091 (Dec.) 1935.

28. Abbott, W. D., and Merkel, B. M.: Acoustic Neuroma Producing Tic Douloureux. J. Iowa M. Soc. 30:465-468 (Oct.) 1940.

A review was made of the records of 96 patients whose trigeminal neuralgia had been cured by temporal section of the sensory root in 100 operations. Findings suggestive of paralytic involvement of the trigeminal nerve or of involvement of neighboring nerve roots or of the cerebellum were absent. In 3 patients residual signs were found of a previous clinically diagnosed cerebral vascular accident, and in 1 evidence of combined sclerosis was noted.

A review was made of the records of 22 other patients in whom a tumor of the cerebellopontile angle or of the anterior portion of the cerebellar hemisphere was verified at operation. None of these patients had suffered pain suggestive of trigeminal neuralgia, although 9 of them had sufficient involvement of the sensory root to produce diminution of sensation in the face and 14 of them had diminished corneal reflexes. Minimal compression of the root in case 1 was followed by tic douloureux, while in other cases extensive stretching and displacement of the root by a huge tumor did not result in pain. Minimal involvement of the root probably is in itself not the cause of the pain. In case 3 a small meningioma which just touched the root did not produce pain, although typical tic developed four and one-half years later. At this time the sensory root was surrounded by arachnoid adhesions. In another patient with a small recurrence of a meningioma of the cerebellopontile angle around the sensory root, tic douloureux did not develop. Although the neoplasm responsible for the neuralgia in 2 instances here was an epidermoid, another huge epidermoid in my series did not produce the pain even though it distorted the sensory root severely.

#### CONCLUSIONS

Cases reported in the literature reveal that while a tumor compressing a peripheral branch or the ganglion of the trigeminal nerve may produce "ticlike" pain, this usually is secondary in importance to the steady background pain and the sensory loss that accompany it. Compression of the sensory root of the nerve by a tumor of the cerebellopontile angle may produce pain and sensory loss indistinguishable from symptoms caused by a tumor of the middle fossa, but involvement of the neighboring nerve roots usually permits differentiation.

A lesion affecting the trigeminal pathways in the temporal fossa or in the cerebellopontile angle may produce pain indistinguishable from that of major trigeminal neuralgia. Such lesions are more numerous in the posterior than in the middle fossa. In my small series, minimal signs of involvement of the adjacent nerves allowed the differentiation of location to be made, but in the second case this did not occur until the morning of operation. Obviously, if these telltale signs had occurred a few days later, the lesion would have been missed and the symptoms attributed to postoperative sequelae. Experience has shown that section of the sensory root by either approach will relieve trigeminal pain, whether it originates peripheral or central to the gasserian ganglion. Although review of the series of cases in which temporal trigeminal rhizotomy was performed showed that signs referable to the posterior fossa were not present at the time of study, some neoplasms of the cerebellopontile angle may go undisclosed to the grave with elderly patients, who presumably die of extraneous causes within a few years of operation. Dandy's large series proves that the association of these lesions is more than coincidental.

Although my limited experience bears out Dandy's greater one that section of the sensory root of the trigeminal nerve by suboccipital approach is safe and is

followed by little morbidity when done by modern neurologic surgeons, it is my impression that the temporal approach is preferable for the elderly, perhaps "poor risk" patient. To the group of persons suspected of having a tumor of the cerebellopontile angle, for whom the posterior approach is indicated, should be added the younger patients with trigeminal neuralgia. In substituting Sjöqvist's<sup>29</sup> trigeminal tractotomy for sensory rhizotomy in the treatment of trigeminal neuralgia, the same criteria in the selection of cases must be used; the cerebellopontile angle should not go unexplored when exploration is indicated. This is possible, since the operation is easily done through a midline incision that is simpler than the larger muscle flap operation.

#### SUMMARY

A tumor compressing a peripheral branch or the ganglion of the trigeminal nerve may produce "ticlike" pain that usually is accompanied by steady background pain, burning and numbness. The pain may pass for that of trigeminal neuralgia.

A tumor of the cerebellopontile angle compressing the sensory root may produce a pain syndrome indistinguishable from that of a tumor of the middle fossa, but symptoms from adjacent nerve roots usually aid differentiation.

A tumor of the cerebellopontile angle may produce pain indistinguishable from major trigeminal neuralgia. Differentiating signs will appear later, but they may be absent at the time of examination and operation.

Tic pain due to a lesion of either the middle or the posterior fossa is relieved by injection of alcohol or temporal section of the sensory root of the trigeminal nerve.

Patients with tic douloureux must be examined carefully for signs referable to a possible lesion of the posterior fossa. If any doubt exists, the rhizotomy should be done via the posterior fossa. Patients younger than the average with tic douloureux deserve the posterior approach.

The posterior approach is safe and results in little morbidity. The temporal approach, in the hands of those more familiar with it, remains the operation of choice for the elderly, "poor risk" patient.

When trigeminal tractotomy is used for relief of tic douloureux, the cerebellopontile angle must be explored in every case presenting any question of a gross etiologic lesion.

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# BILIARY DYSKINESIA

ROLE PLAYED BY A REMNANT OF THE CYSTIC DUCT

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The problem of persistence of typical preoperative symptoms after cholecystectomy for supposed cholecystic disease is well known and extremely perplexing. Probably because their cause is not known, a voluminous literature containing many conflicting theories on the subject has appeared. The symptom complex has been given many names, best known of which are biliary dyskinesia,<sup>1</sup> biliary dyssynergia and postcholecystectomy syndrome.

The purpose of this study was to survey an obscure aspect of the problem, namely, the role played by a remnant of the cystic duct and the effect of its removal. The material was obtained from a review of 44 cases in which operation was performed at the Mayo Clinic in the years 1910 to 1940 inclusive because of persistence of symptoms after cholecystectomy. These are, of course, only a small proportion of the cases in which exploratory operation was performed for such symptoms in that period, but in each of these 44 cases the surgeon remarked on the presence of an enlarged remnant of cystic duct and removed it. In all but 2 of these cases the patients were carefully followed.

It has come to be generally agreed that cholecystectomy when performed with proper and adequate indication is a remarkably successful operation. If stones are present, permanent benefit is obtained in 80 to 95 per cent of cases, and only slightly less satisfactory are the results obtained by removal of noncalculous gall-bladders in which there is evidence of advanced disease.<sup>2</sup> The presence of stones is evidence of disease, and in cases in which there is an adequate history of biliary distress cholecystectomy usually is indicated and offers a good prospect of permanent cure. Whipple<sup>3</sup> reported that the procedure failed to relieve symptoms in only 1.8 per cent of such cases. As the indications for cholecystectomy have become less rigid, less favorable results have been reported. It is undoubtedly true that erroneous diagnosis may unjustly indict the gallbladder and after its ill

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advised removal symptoms may persist in spite of the operation and not because of it. This is true in such a group of cases as those which constitute a portion of the present study, and, as will be shown, the majority of the patients have no striking symptoms of biliary distress and usually consult a physician because of vague indigestion.

#### CAUSES OF THE POSTCHOLECYSTECTOMY SYNDROME

The persistence of symptoms after cholecystectomy occurs too frequently to be disregarded. The largest contributing factor probably is erroneous diagnosis. It is often truly difficult to distinguish functional biliary distress from that of organic origin. Ill advised operation also is an etiologic factor. Weir and Snell<sup>4</sup> have said that the inflammatory or degenerative residua of cholecystic disease constitute a leading cause for the persistence of symptoms. Severe cholecystitis is usually accompanied by a certain amount of hepatitis, cholangitis and pancreatitis. Although the inflammatory reaction in the gallbladder may be sufficient to produce the typical distress, the residual inflammation of the biliary tract, if not resolved, may account for an unsatisfactory result. Stricture of the extrahepatic bile ducts may be another source of distress. It is relatively easy to injure them during cholecystectomy, and although complete stricture would result in jaundice or a biliary fistula, incomplete or partial stricture, with its attendant inflammatory reaction, may account for some instances of persistent distress. Residual stones or putty-like material in the common bile duct is a well known cause of recurrent colic and jaundice. Hill's<sup>5</sup> review of the literature, which emphasized the subject of reciprocal innervation of the musculature of the wall of the gallbladder and the sphincter of Oddi, opened the discussion of the cause of biliary colic. In some cases in which the patients are hyperirritable, obscure dyskinesia or dyssynergia of the ductile system, combined with malfunction of the sympathetic and parasympathetic nervous systems, may account for postcholecystectomy colic. Angulation of the duodenum by attachment to the denuded gallbladder fossa also may conceivably cause a certain amount of postoperative flatulence and vague epigastric distress. Last of all, Schmieden and Rhode<sup>6</sup> first called attention to the part played by lesions of the cystic duct in cholecystic disease. Cole and Rossiter<sup>7</sup> lately have reawakened interest in this phase of the problem. They listed the possible lesions responsible for obstruction of the cystic duct (table 1) and called attention to the fact that the fundus of the gallbladder at the time of cholecystectomy may appear entirely normal, just as in the reported cases of biliary dyskinesia, but the cystic duct may be obstructed, kinked or bound down by inflammatory reaction and be the cause of the distress. They said that acute inflammation of the cystic duct is a common occurrence and pointed to the presence of brawny edema, adhesions and even small abscesses about the cystic duct as evidence.

Cole and Rossiter reported 7 cases of cholecystic disease in which the symptoms were typical, but although at cholecystectomy the walls of the fundus of the gall-

4. Weir, J. F., and Snell, A. M.: Symptoms That Persist After Cholecystectomy: Their Nature and Probable Significance, *J. A. M. A.* **105**:1093-1098 (Oct. 5) 1935.

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7. Cole, W. H., and Rossiter, L. J.: The Relationship of Lesions of the Cystic Duct to Gall Bladder Disease, *Am. J. Digest. Dis.* **5**:576-586 (Nov.) 1938.

bladder appeared essentially normal one or more of the lesions listed in table 1 were found in the region of the cystic duct. Cholecystectomy relieved the symptoms in all of these cases. Had the diseased cystic ducts not been recognized and removed, the patients may well have become "neurotic" and the so-called post-cholecystectomy syndrome might have developed. This thought gave impetus to the present study.

Investigation of the anatomy involved demonstrated the possibility of such an oversight in surgical technic, because there is probably no portion of the body more subject to anomalies and wide variation than the gallbladder and its cystic duct. Operation in this region lends itself readily to the possibility of amputating the gallbladder above an anomalous cystic duct and leaving a good-sized stump which may dilate, remain inflamed or contain calculi. The cystic duct is usually about 3 mm. in diameter, that is, half the diameter of the hepatic duct, but it is 31 to 37 mm. in length. It begins at the neck of the gallbladder, which is curved medially toward the porta hepatis in the form of the letter "S." Around the interior of its cavity at this point are a series of crescentic folds, which are placed spirally and form the valvula spiralis of Heister. The cystic duct pursues a course

TABLE 1.—*Lesions Responsible for Obstruction (Partial or Temporarily Complete) of the Cystic Duct\**

- 
- |    |  |
|----|--|
| 1. | Stenosis produced by surrounding adhesions                   |
| 2. | Stenosis produced by a thickened wall                        |
|    | a. Owing to acute inflammation                               |
|    | b. Owing to diffuse fibrosis                                 |
| 3. | Congenital or inflammatory twists or kinks                   |
| 4. | Congenital or inflammatory lesions of the valves of Heister  |
|    | a. Fibrous strands   |
|    | b. Local deposition (nodules) of fibrous tissue              |
|    | c. Stricture caused by scar                                  |
|    | d. Valve-like anomalies                                      |
| 5. | Stone in the duct  |
| 6. | Tension induced by enlarged liver                            |
| 7. | Compression or filling defect caused by tumor or lymph nodes |
| 8. | Anomalous hepatic or cystic artery                           |
- 

\* As determined by Cole and Rossiter.<sup>7</sup>

backward and medially to join the hepatic duct and form the common bile duct. There are many variations in this course and many irregularities in the shape, situation and size of the cystic duct.

In our study it soon became apparent that the 44 cases could be divided into two well defined groups. The first group includes 18 cases in which calculi were found in the common bile duct or in the stump of the cystic duct when operation was performed to relieve the persistent distress which occurred after cholecystectomy. In 11 of the 18 cases the calculi were found in the common bile duct and in 7 the calculi were found in the stump of the cystic duct (table 2). The second group includes 26 cases in which no calculi were found at the second operation. The enlarged remnant of the cystic duct was removed in all of the 44 cases (table 2).

#### GROUP I

In the 18 cases which comprise this group, 13 of the patients were women and 5 were men. When the operations were performed for the relief of the persistent distress, the ages of the patients ranged from 24 to 66 years. In 16, or 89 per cent, of the cases which comprise this group, definite gallbladder colic had been present before the primary operation on the biliary tract was performed. The colic had been associated with severe attacks of nausea and vomiting and residual sore-

TABLE 2.—*Clinical and Pathologic Observations and Treatment*

	Subsequent Operation														Results Based on Follow Up Data in 10 of 11 Cases*
	Symptoms of Cholecystic Disease Before Cholecystectomy				Cholelithiasis Found	Appearance of Persistent Symptoms After Cholecystectomy		Hepatitis and Pancreatitis	Pathologic Observations		Operative Procedure				
	Char-acter-istic		Mild or Absent			Early	Late		Inflammation of Stump of Cystic Duct	Duodenal Adherent to Gall-bladder Fossa	Removal of Stump of Duct and Gall-bladder When Present	Drainage of Cystic Duct and Common Bile Duct			
	Number	Per Cent	Number	Per Cent											
Group 1:															
Stone in common bile duct *	11	25	0	2	0	0	2	1	1	5	2	11	11	11	(Follow-up data in 10 cases; complete relief in 6 cases; no relief in 4 cases, including the 2 in which symptoms were mild or absent)
Stone in stump of cystic duct *	7	16	7	0	0	1	0	1	5	..	2	7	7	0	(Follow-up data in 6 cases; complete relief in 5 cases; no relief in 1 case; 1 patient died seven years later)
Group 2:															
Cholelith not present*	20	50	10	7	19	10	10	11	5	10	5	20	20	22	(Follow-up data in 21 cases; complete relief in 11 cases; no relief in the 7 cases in which symptoms were mild or absent)
Total.....	41	100	35	9	31	20	18	10	11	21	9	41	41	39	

\* When operation was performed for the relief of symptoms that persisted after cholecystectomy.

\* When operation was performed for the relief of symptoms that persisted after cholecystectomy.



ness had occurred in the right upper quadrant of the abdomen. In 3 of these cases the patients had had repeated attacks of chills and fever, and in 2 of the 16 cases jaundice had been noticed on at least one occasion. In 15, or 83 per cent, of the cases in this group, cholecystography had demonstrated the presence of calculi. In the 2 remaining cases, the patient had not had symptoms that were characteristic of cholecystic disease, but in 1 of them roentgenologic examination had disclosed cholelithiasis. In 1 of the 2 cases the patient had complained of vague, mild, rather constant indigestion, but in the other, in which stones were demonstrable roentgenologically, the patient had not had any symptoms. Cholecystectomy was warranted in at least 16 of the 18 cases. If the presence of biliary calculi is sufficient indication for cholecystectomy, the operation was indicated in all but 1 of these cases.

In 2 of the 18 cases, cholecystostomy had been performed several years before the patients were subjected to cholecystectomy. In the remaining 16, cholecystectomy was the primary operative procedure. In the 11 cases in which a subsequent operation disclosed a stone in the common bile duct, the interval between cholecystectomy and the appearance of the persistent postoperative distress was less than one month in 9 cases and two to five years in 2. Jaundice occurred in only 5 of these cases, but severe pain occurred in all. In these 11 cases, choledochostomy was performed and the enlarged stump of the cystic duct was removed. Microscopic examination disclosed subacute or acute inflammation of the stump of the cystic duct in 9 of the 11 cases. The presence of a stone in the common bile duct probably is sufficient to explain the persistent symptoms, but the active inflammation of the stump of the cystic duct is significant.

As stated previously, in 7 of the cases in group 1 a stone was found in the stump of the cystic duct when an operation was performed for the relief of the distress which occurred after cholecystectomy. The distress occurred immediately after cholecystectomy in only 1 of the 7 cases. In the remaining 6 cases the patients felt greatly relieved for sixteen months to nine years after cholecystectomy had been performed. The history was suggestive of biliary colic in only 1 case. In the other cases the patients complained of soreness in the region of the gallbladder, mild epigastric distress and occasional nausea and vomiting. In 5 of these 7 cases, the stump of the cystic duct not only contained a stone but also was subacutely inflamed. In 6 of the 7 cases, the common bile duct was explored at the time of the subsequent operation.

In all of the 18 cases in group 1 the duodenum was adherent to the gallbladder fossa. The operative notes did not mention severe angulation of the duodenum.

In 10 of the 11 cases in which a stone was found in the common bile duct, a careful effort was made to obtain follow-up data. The subsequent operation relieved the persistent distress in only 6, or 60 per cent. Cholecystectomy had been indicated in all 6. In the 2 cases in which the indications for cholecystectomy may be subject to question, the subsequent operation failed to relieve the persistent distress, although a stone was removed from the common bile duct.

In 2 of the 4 cases in which the subsequent operation failed to relieve the persistent distress, the patients returned to the clinic on several occasions and complained of "the same old distress and pain" for which "everything that had been tried" had failed. In 2 of these cases, other operations have been performed. In 1 of these choledochoduodenostomy was performed within a year after cholecystectomy for relief of the distress. Seven years after the last operation the patient still complained of attacks of nausea and vomiting, vague epigastric distress and dyspepsia. In the other case, an exploratory operation was performed ten months after the first operation for the relief of the distress that occurred after cholecys-

ectomy. No calculi were found at operation. A T tube was left in the common bile duct for a long time. The distress continued, and within two months the common bile duct was explored again. Four years after the last operation the patient was having attacks of bloating and distress about twice a month.

In 1 of the 7 cases in which operation for the persistent distress disclosed a stone in the stump of the cystic duct, the patient died of cardiac failure seven years later, and we were unable to obtain any information about the results of the operation. Follow-up data are available in the remaining 6 cases. The results were satisfactory in 5, or 83.3 per cent. In 4 the persistent distress disappeared after the operation and the patients were in good health when last heard from. In 1 of the 6 cases the patient has had at least two attacks of nausea, vomiting and severe indigestion which were similar to those she had experienced before the last operation.

Analysis of the results obtained in the cases in group 1 revealed one outstanding fact, namely, that the subsequent operation relieved the persistent distress in a large proportion of cases in which the indications for cholecystectomy appear to have been adequate.

#### GROUP 2

In the 26 cases which comprise this group, 20 of the patients were women and 6 were men. When the operations were performed for the relief of the persistent distress, the ages of the patients ranged from 25 to 66 years. For several years before cholecystectomy had been performed, the patients had had symptoms which had been ascribed to disease of the biliary tract. In 5 of the cases the patient had been subjected to cholecystostomy before cholecystectomy was performed.

In the 19 cases in which stones were found in the common bile duct, in the remnant of its cystic duct, the past history indicated that the patient had had cholecyctic disease before cholecystectomy was performed and the operation appears to have been indicated. All of the 19 patients had had typical attacks of indigestion, which had been accompanied by nausea and vomiting, and 10 had had pain in the right upper quadrant of the abdomen, which had been severe enough to require medication. In 4 of the cases jaundice had followed one of the attacks and in 2 the patients had had attacks of chills and fever. In all of the 19 cases, calculi were found in the gallbladder when cholecystectomy was performed. In 7 of the 26 cases in the group, the patients had had few symptoms which would suggest sufficient disease in the gallbladder to indicate cholecystectomy. The symptoms had not been severe in any of these cases, and in most of them the distress had been minimal. Cholecystography had failed to reveal any calculi, and none were found when cholecystectomy was performed. Colic, jaundice, chills or fever had not occurred. The most frequent symptoms had been dyspepsia, pyrosis and constipation, and these had been noted for several years. It is probable that the diagnosis of cholecyctic disease was erroneous and that the postoperative distress occurred in spite of, and not because of, cholecystectomy.

In 5 of the 7 cases in which calculi were not found in the gallbladder, the symptoms recurred immediately after cholecystectomy was performed, that is, before the patients were dismissed from the hospital. In 11 of the 19 cases in which calculi were found in the gallbladder, the symptoms recurred soon after cholecystectomy was performed. The symptoms were similar to those which had occurred before operation. However, colic occurred in fewer cases than it had before operation. Jaundice was said to have occurred in 2 cases, but this could not be verified. The most frequent symptoms were persistent soreness in the right upper quadrant of the abdomen, bloating, dyspepsia, flatulence, pyrosis and constipation. Vague

and atypical pain, which was present more or less constantly in the right upper quadrant of the abdomen, was almost a constant feature.

In all of the cases in this group, subsequent operation disclosed enlargement of the stump of the cystic duct. Microscopic examination of the sections of the stump disclosed subacute inflammation in 5 cases, acute inflammation in 16 and chronic inflammation in five (table 2). Although the common bile duct was enlarged in all of the cases, the enlargement was no greater than that usually observed after cholecystectomy. Mild pancreatitis or hepatitis or both was observed in 11 of the 26 cases in this group. No severe inflammation of the pancreas, liver or bile ducts was observed. In all of the cases the duodenum was adherent to the gall-bladder fossa, but severe angulation was not noted. In a few cases the surgeon expressed the opinion that this mild distortion of the duodenum was sufficient to produce symptoms.

In analyzing the results of subsequent operation in this group of cases, the most striking feature was the condition of the patients in the 7 cases in which the indications for cholecystectomy may be subject to question. Although one to seventeen years had elapsed since operation was performed for the relief of the distress that had occurred after cholecystectomy, the patients still complained of the "same old distress" and 6 requested that further surgical procedures be employed. The other patient induced another surgeon to perform an exploratory laparotomy for "adhesions" three years after the stump of the cystic duct had been removed at the clinic. Since the last operation, she has been seen repeatedly at the clinic, and the persistent distress is still present after twelve years.

In the remaining 19 cases in this group, the indications for cholecystectomy appear to have been adequate. Follow-up data are available in 17. In 11, or 64.7 per cent, the subsequent operation relieved the distress. In 6, or 35.3 per cent, the distress was still present when the patients were last seen at the clinic.

#### COMMENT

Follow-up data were available in 40 of the 44 cases in this series. In 31 of the 40 cases, the indications for cholecystectomy may be said to have been adequate. In 22, or 70.9 per cent, of the 31 cases, the persistent distress was relieved by a subsequent operation which consisted of removal of the stump of the cystic duct and removal of calculi when found in the common bile duct or in the stump of the cystic duct. A subsequent operation failed to relieve the distress in all of the 9 cases in which the indications for cholecystectomy may be subject to question. Considering the entire group, about half of the patients were relieved by the subsequent operation.

#### SUMMARY AND CONCLUSIONS

Biliary dyskinesia, regardless of its cause, is a distressing problem. The two most probable causes of its occurrence are (1) erroneous diagnosis of cholecystitis and ill advised removal of the gallbladder with the persistence of some functional disorder of the choledochus sphincter and (2) residual inflammatory disease of the liver, pancreas or ductile system. The possibility that some inflammatory or mechanical lesion of the cystic duct may cause typical symptoms of cholecystic disease suggests that a similar lesion in a remnant of cystic duct may be the obscure cause of persistent pain after cholecystectomy. In many cases the removal of this remnant of cystic duct has been coincident with choledochostomy and choledocholithotomy. If the original operation was performed on the basis of adequate historical or roentgenographic indications or both, about 70 per cent of the patients

have been found to obtain relief of persistent symptoms by the second operation in which the cystic duct with or without stones is removed.

In this series of 44 cases all specimens of cystic duct removed showed evidence of disease; in 35 cases (79 per cent) there was evidence of recent inflammation.

In a series of 26 cases of biliary dyskinesia in which at the second operation only an enlarged inflamed remnant of cystic duct was incriminated and removed, approximately 65 per cent of the patients were relieved of their symptoms, provided that the first operation was well advised and necessary. If the first operation was performed on the basis of inadequate indications, 100 per cent failure resulted from the secondary operations in which only drainage of the common bile duct or removal of a remnant of cystic duct could be accomplished.

Too great stress cannot be placed on the importance of operating only in those cases in which there is definite and conclusive clinical or roentgenographic evidence of disease of the biliary tract. At the time of operation, meticulous care must be exercised in order to avoid damage to the common bile duct but at the same time all but a very small remnant of the cystic duct should be resected. In those cases in which the patient unfortunately experiences persistence or recurrence of pain after cholecystectomy and in which reoperation is deemed necessary, diligent search should be made for a remnant of the hepatic duct whether or not calculi are suspected in the common bile duct.

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# RETICULOCYTOSIS FOLLOWING ABLATION OF FRONTAL CEREBRAL CORTEX

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In the course of studies on the evidences of autonomic imbalance which follow removal of cerebral cortex,<sup>1</sup> it has been possible to show that some of these effects are specifically due to frontal injury. One of these, as indicated in a preliminary report,<sup>1f</sup> and the easiest to follow is reticulocytosis. The present investigation is concerned with the latency and degree of this response of the blood as engendered by a frontal lesion.

## EXPERIMENTS

Adult dogs which had been examined for freedom from parasites were placed on a standard diet and, after a preliminary observation period of thirty days during which the weight and reticulocyte count were frequently checked to ascertain that stability was being maintained, were subjected to simultaneous bilateral removal of all frontal cerebral cortex, as far back as and including the postsigmoid gyrus. Care was taken to avoid infringing on the caudate nuclei or the ventricular system. The olfactory tracts and the piriform cortex were also left intact. Such an operation can be done with insignificant loss of blood, but since an intracranial factor other than interference with the function of the frontal lobes might be considered responsible for the results obtained, control animals were subjected to bilateral removal of an equivalent amount of occipital tissue. Four series of 5 animals each were studied, 1 animal in each series being a control. No appreciable reticulocytosis occurred in the animals with occipital lesions but in all the animals with frontal lesions the reticulocyte count increased. The maximum increase was 7.1 per cent (from 0.3 to 7.4 per cent) (chart 1) and the minimum 3.75 per cent (from 4.25 to 8.0 per cent) (chart 1.). In practically all cases the response to removal of frontal cortex consisted of an almost immediate initial shower of reticulocytes and, after a latent period of about four days, a maximum response which was succeeded by lesser showers and some slight instability.

## COMMENT

Bilateral removal of frontal cortex is usually followed by at least a temporary inability on the part of the animal to feed itself. In spite of careful hand watering and feeding there is generally some loss of weight, and it might be imagined that the reticulocytosis is due to hemoconcentration. Reference to the records of weight, however, revealed no inverse relation between loss of weight and increase in reticulocytes. Moreover, if hemoconcentration were the cause of the increase there

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should have been a simultaneous increase in the number of the other formed elements of the blood. Reference to the erythrocyte count failed to disclose any such parallelism but revealed instead a rapid drop in the number of red cells. Further, it was observed that the reticulocyte showers were regularly preceded by the appearance of unusual numbers of hemokonias. These elements were first observed by the technician assisting with the work (Mrs. Cornelius Elsasser), and their appearance suggested genuine hemopoietic stimulation.

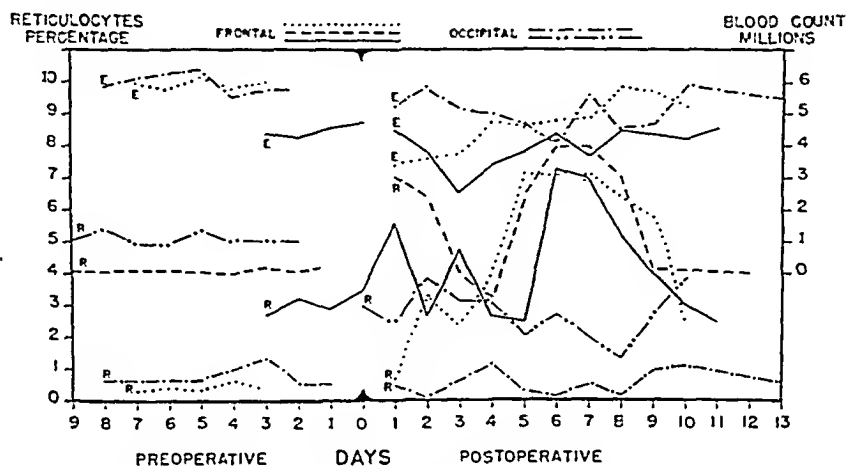


Chart 1.—Comparison of the effects of typical frontal (3 dogs) and occipital (2 dogs) operations. It will be observed that the animals with occipital lesions showed no appreciable reticulocytosis but that the reticulocyte response to frontal operation consists of a slight, immediate, unsustained rise which is followed by a more evident rise occurring after a latent period of about four days. Subsequent instability may be expected (chart 2). E, erythrocytes; R, reticulocytes.

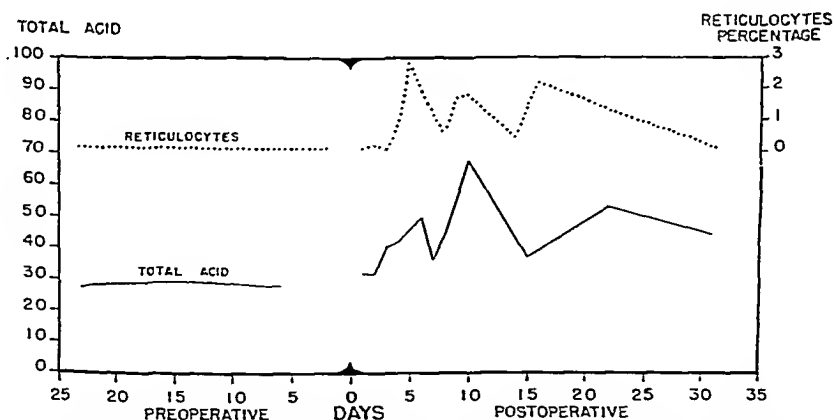


Chart 2.—Comparison of the reticulocyte and the gastric acidity curve of the same animal. While these are roughly parallel, it cannot be said that the hemopoietic response depends on the changes in acidity, since the former generally lags slightly behind the latter.

In previous experiments<sup>1d</sup> I have encountered a relative peripheral anemia following cortical removal. It is also known that cortical removal may be followed by blushing of the gastric mucosa, splenomegaly and increased response to epinephrine,<sup>1e</sup> circumstances which argue for visceral erythrocytic stagnation and may explain the peripheral anemia. In the present experiments the erythrocyte count usually dropped after frontal operation (but not after occipital operation),

sometimes declining gradually for two or three days. It is not inconceivable that visceral vasostasis may be the indirect cause of the reticulocytosis since it produces peripheral anemia, but another factor remained to be considered. By some mechanism, the nature of which is not precisely clear, removal of frontal cortex may produce gastric hyperacidity,<sup>14</sup> and it is worth noting that the latent period of the maximum reticulocyte response to removal of such cortex is approximately the same as that after the administration of liver or gastric extract (three to five days). I therefore decided to follow the time relationships between the reticulocyte and the acid response after bilateral removal of frontal cortex in an animal with a previously prepared gastric fistula. The result is shown in chart 2. The characteristics of the acid curves were irregular but suggestive of those of the reticulocyte response. Simultaneous study of total acid and reticulocyte curves showed a rough parallelism, but the rise in gastric acidity generally lagged slightly behind the reticulocyte response and cannot therefore have stimulated it. Presumably both results are due to some common cause rather than dependent on each other.

#### CONCLUSION

Removal of frontal cerebral cortex from the dog produces a reticulocyte response not seen after other cortical operations. This is not the result of injury to subcortical nuclear areas, nor is it due to hemoconcentration.

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# REPAIR OF LARGE CRANIAL DEFECTS

REPORT OF A CASE IN WHICH A LARGE CRANIAL DEFECT WAS  
REPAIRED BY A GRAFT FROM THE ILIUM

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From a survey of the literature<sup>1</sup> it appears that the fact that a large amount of bone may be obtained from the ilium as a transplant for repairing a cranial defect is not well known. The case to be reported demonstrates that a large defect of the skull may be repaired by utilizing almost the entire outer table of the ilium with only temporary impairment of function of either the pelvic bone or the muscles detached from it.

E. B. P., a 26 year old man, was referred by Dr. Thomas C. Douglas to the University of Chicago Clinics on Oct. 15, 1941. His complaint was of a bony swelling, which had been present in the right parietotemporal region for two and a half years. He stated that the mass had remained stationary in size for two years but that for the past five months it had increased in size. On May 30, 1941 he had a severe headache accompanied by a transitory slight impairment of memory. In July headaches of a sharp knifelike character developed, especially over the right parietal region. Often they were accompanied by periods of transient dizziness. The day before his admission to the hospital he experienced numbness in the fourth and fifth fingers of his left hand. This gradually spread to the rest of the hand and to the forearm. He described his arm as "being strange but not numb." At the same time he noted that the left side of his face was numb and that his tongue felt thick and difficult to maneuver. He had no muscular weakness.

Physical examination revealed a hard nonfluctuant mass, measuring 8 by 8.5 cm., over the right frontoparietal area and merging with the surrounding bone. No bruit was audible. Neurologic examination revealed no abnormality except that the left arm did not swing as much as the right.

Lateral roentgenograms of the skull demonstrated a large area of sclerosis, measuring about 9 cm. in diameter, in the right frontoparietal region. The central part of the sclerotic area was less dense than the periphery. Radiating toward the center were dense bony spicules. Tangential views of the sclerotic area showed lines of density radiating from the inner table and matrix peripherally into the mass, which had elevated and markedly thinned the outer table. The skull was approximately 4 cm. in thickness. The inner table appeared to be intact (fig. 1).

The blood and the urine were normal, and the Wassermann and Kahn reactions of the blood were both negative.

On October 24 Dr. A. E. Walker performed a right frontal craniectomy and removed a tumor, diagnosed as meningioma. A horseshoe incision was made with the base in the temporal region. The incision anteriorly followed the hair line and posteriorly was 1 to 2 cm. outside the margin of the hyperostosis. The tissues of the scalp were quite vascular, but the

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1. (a) Maclair, P.: Greffes crâniennes, *Arch. gén. de chir.* **10**:302, 1914. (b) Phemister, D. B.: Personal communication to the author. (c) Pickerill, P.: A New Method of Osteoplastic Restoration of the Skull, *M. J. Australia* **2**:228, 1931. (d) Money, R. A.: Osteoplastic Restoration of the Skull, *ibid.* **2**:269, 1932. (e) Klages, F.: Plastische Deckung grösser Schädeldefekte aus dem Beckenkamm, *Zentralbl. f. Chir.* **28**:1580, 1939. (f) Rehn, cited by Klages. (g) Klapp, cited by Klages. (h) Naffziger, H. C., in discussion on Grant, F. C., and Norcross, N. C.: Repair of Cranial Defects by Cranioplasty, *Ann. Surg.* **110**:511, 1939. (i) Kolodny, A.: Osteoplastic Repair of Cranial Defects, *Am. J. Surg.* **46**:365, 1939. (j) Naffziger, H. C.: The Restoration of Defects of the Skull, *Ann. Surg.* **104**:321, 1936. (k) Grant, F. C., and Norcross, N. C.: Repair of Cranial Defects by Cranioplasty, *ibid.* **110**:488, 1939.



bleeding was controlled without great difficulty. Perforations were placed so that two saw cuts could be made both anteriorly and posteriorly outside the involved bone. The medial limb of the bone flap was rongeuired away, since it lay almost over the superior longitudinal sinus. The scalp was reflected from the hyperostosis, and the bone flap was fractured. The temporal muscle was seized with a Kocher forceps and cut so that the hyperostotic bone was removed in one piece. The cut edge of the temporal muscle was sutured to control bleeding. The exposed dura was quite firm over an area about 4 by 5 cm. in diameter, although there was relatively little bleeding from this area. The adjacent dura appeared normal in consistency. The dura was incised about 1 cm. outside the firm area, and this incision was made in normal dura mater around the entire circumference of the tumor. The tumor was carefully dissected from the brain tissue and delivered from its bed. On the

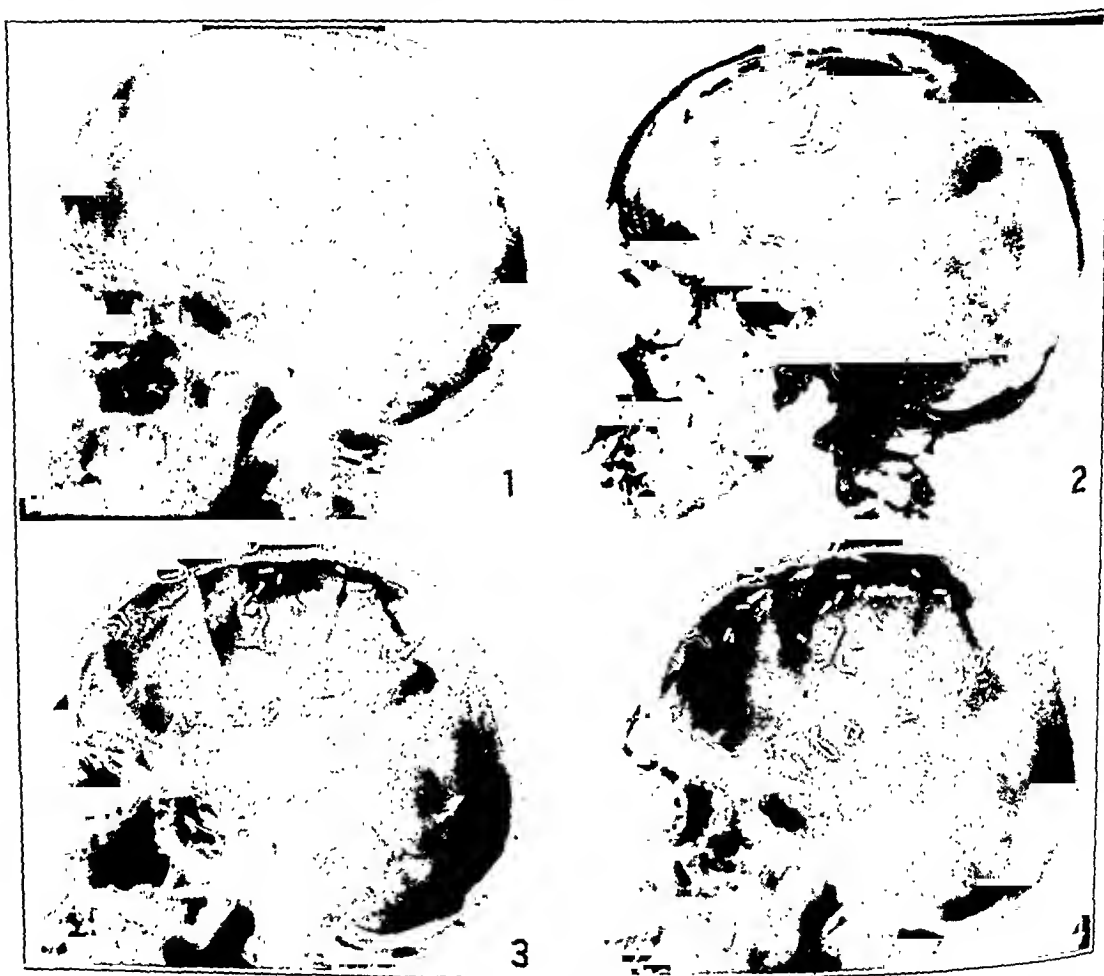


Fig. 1.—Right lateral roentgenograms of the skull taken as follows: (1) before operation, showing the large area of hyperostosis in the right frontal region. (2) after the first operation, showing the large defect following the removal of the tumor. The size of the tumor may be estimated by the outer ring of silver clips. The central group of clips are in the vascular bed of the tumor. (3) after the second operation, showing the defect filled with bone grafts from the external table of the ilium. (4) six and one-half months after the second operation, showing some absorption of the osseous grafts.

medial border it was found to be attached to the dura mater along the longitudinal sinus. It was cut away after the margin of the sinus had been clipped. A branch of the rolandic vein was clipped. On inspection the tumor seemed to be completely removed except along the anterior margin of the bony defect. Accordingly, 1 to 2 cm. of bone was rongeuired from this region. A piece of fascia lata shaped to the dural defect had been removed from the right thigh; it was sutured in place with black silk. The skin was closed with two layers of sutures.

The pathologic specimens consisted of the hyperostotic bone, measuring 11.3 by 8.5 by 4.5 cm. and weighing 263 Gm., and a mass of tumor tissue attached to the dura mater, measuring 7 by 6 by 4 cm. and weighing 55 Gm.

The bone was covered on its outer convex surface with muscle and periosteum and was firm except for a soft central area 5 to 6 cm. in diameter. The concave or inner surface of the bone was roughened by fine bony trabeculations. Sectioning through the center of the bone revealed a fleshy mass 1 to 2 cm. in thickness between the bony tables.

Numerous bony spicules, usually radiating to the dome, passed through this mass. The central portion of the external table was composed almost entirely of soft tumor tissue.

Sections through the bone showed marked osseous proliferation with multiple fine bony spicules. The young bone was poorly calcified. Between the bony spicules was an intertwining mass of connective tissue, tumor cells with the same characteristics as those in the tumor proper and small amounts of normal marrow. The periosteum could be traced from the margin of the hyperostosis to its dome. The hyperostosis was infiltrated with tumor tissue, which had not penetrated the periosteum at any point.

The tumor was covered on one side by thickened trabeculated and roughened dura mater. On the opposite pole it was nodular, but the surfaces of these excrescences were smooth. Sectioning the tumor revealed coarse trabeculation with a tendency toward radiation from the dural surface. Its firm coarse-grained surface contained numerous small brown hemorrhagic areas.

The tumor was composed of lanceolate cells with medium-sized nuclei, which varied from oval to round. The cells were irregularly arranged parallel to each other or in whorls. In areas the cells were separated by clear spaces, presumably edema. There were many hyalinized areas scattered throughout, a few of which had calcospherites. In a few places the cells were enlarged and had eccentric nuclei and honeycomb cytoplasm, probably representing fatty degeneration. Reticulin was seen only surrounding the blood vessels.

The pathologic diagnosis was psammomatous meningioma with hyperostosis.

On November 8 bone was transplanted from the ilium to the defect in the skull. Dr. Walker reflected the scalp. This exposed a large cystic cavity with a smooth wall, bounded internally by the fascial transplant and externally by the subcutaneous tissue. The cavity contained xanthochromic fluid, which escaped as the cutaneous flap was reflected. The bony margin of the cavity was freshened, and the periosteum in the anteroinferior portion of the incision was cut away. Since at the previous operation the periosteum in this region was slightly thickened, and since microscopic examination of a specimen from this area had revealed evidence of tumor, the periosteum was removed to normal tissue. A rubber patch was shaped to fit the defect in the skull.

Dr. D. B. Phemister made a large horseshoe-shaped incision along the crest of the right ilium. This extended downward 4.5 cm. from the anterior and posterior iliac spines. The muscles were stripped from the entire side of the ilium. There was much oozing, but the bleeding points were controlled by catgut ligatures. The patch of rubber tissue cut to the size of the defect in the skull was laid on the side of the ilium with its long axis placed anteroposteriorly. With a narrow chisel, the graft to be cut was outlined. It was divided into three portions by making two cuts running longitudinally with the body, about one third of the distance from either end (fig. 2). With a thin, wide-beveled chisel, the tabula externa of the anterior graft, extending forward to the anterior spine, was chiseled off from above downward. This graft was slightly curved as it was cut away. The middle graft was cut from above downward in the same way, its base lying anteriorly just above the acetabulum. The entire thickness of the ilium was removed at the normally thin region; elsewhere the line of division passed through spongy bone. The posterior graft was cut from above downward, its posterior limits extending to within 2 cm. of the posterior inferior spine. There was oozing from the denuded bone, which comprised at least four fifths of the lateral surface of the ilium. The flap was reflected, and the deep fascia of the gluteal muscles was sutured along the iliac crest with interrupted chromic catgut sutures to the muscular attachments above. One Penrose drain was inserted posteriorly. The subcutaneous tissue was sutured with plain catgut and the skin with interrupted silk.

The first bone graft was fitted into place in the anterior third of the cranial defect. Perforations were made in the graft and in the margins of the defect in the skull, and the graft was held in place with silver wire. Each of the subsequent grafts was similarly fitted into the defect, the inner surface of the graft being exposed and the smooth external surface being opposed to the fascia lata (fig. 3). The skin was turned down over the roughened surface of the grafts and closed with interrupted black silk sutures, one layer being placed in the subcutaneous tissue and one layer in the skin.

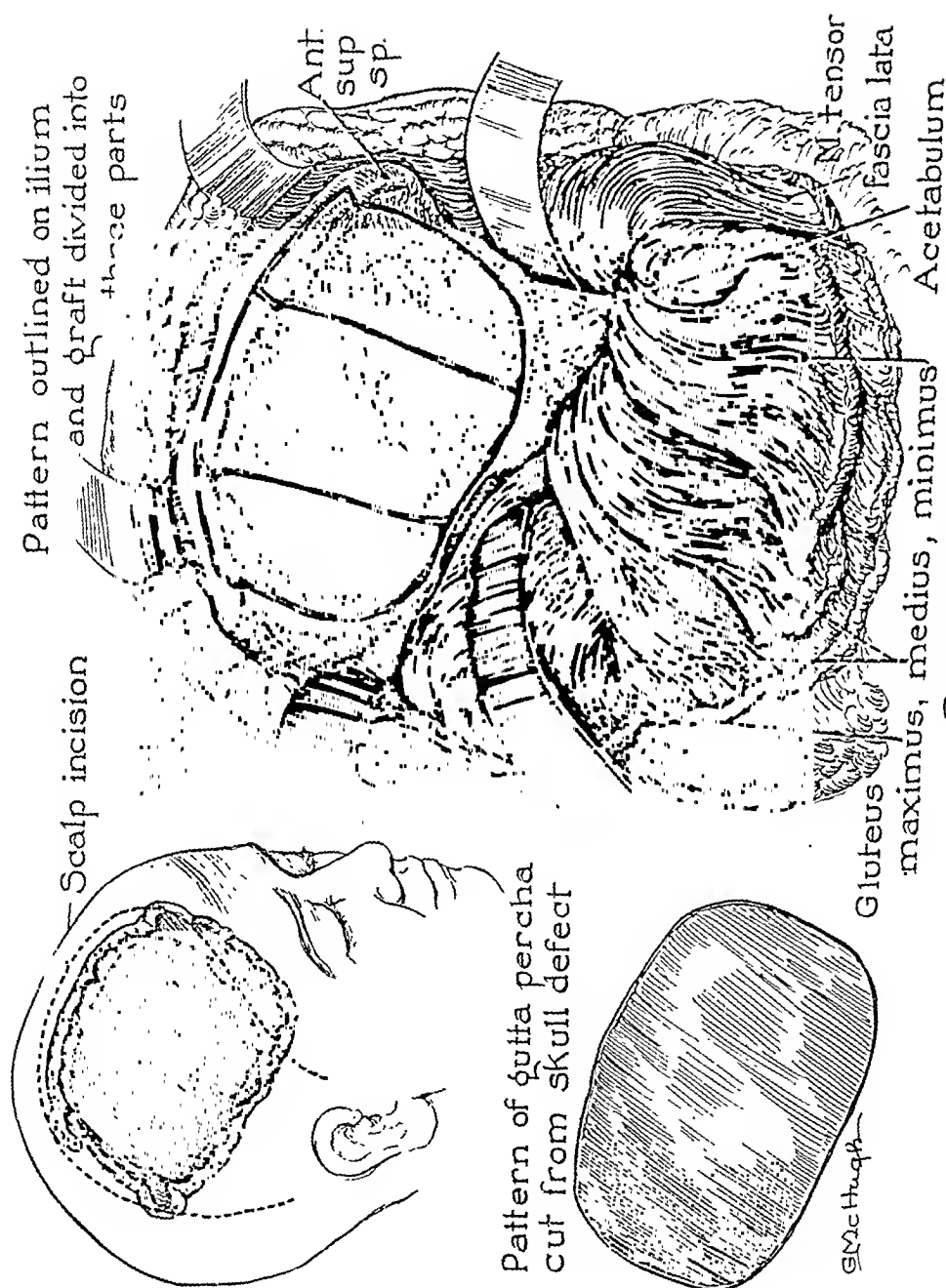


Fig. 2.—Sketches to show the operative procedures used in cranioplasty using grafts from the ilium. In the upper left hand corner the bony defect is shown, with the dural defect closed by fascia lata.

The right leg was placed in an aluminum posterior splint with a cross bar rest to prevent external rotation while the muscles were becoming reattached. The postoperative course was uneventful.

In four weeks the patient was able to walk with the aid of crutches. Two months after the second operation he had some weakness of the abductor and internal rotator muscles of the thigh. Five months after the operation he was allowed to walk without crutches.

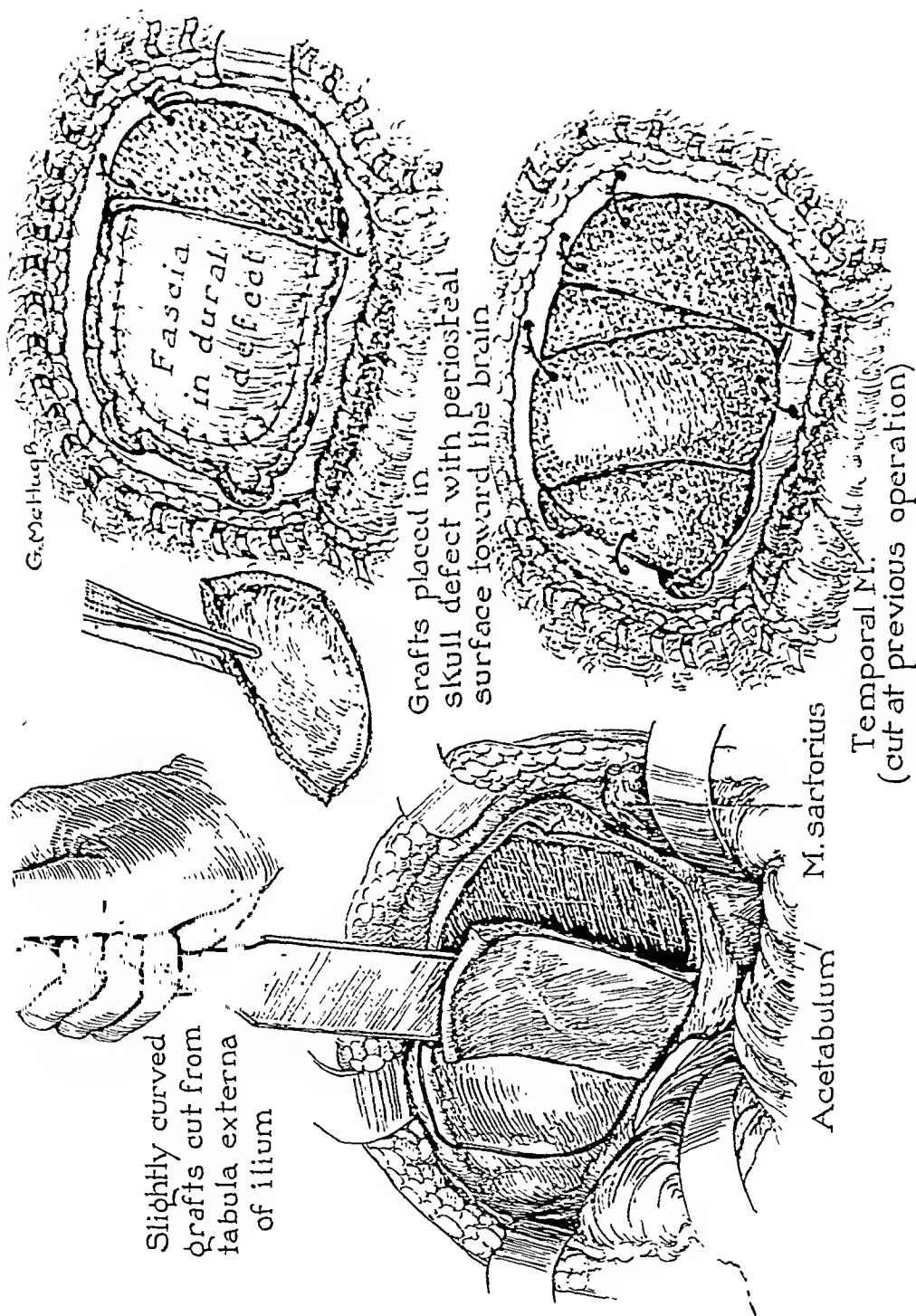


Fig. 3.—The placing of the bone grafts in the cranial defect.

There was still, however, slight weakness of the internal rotator muscles of the thigh. The cranial defect was well filled. Roentgenograms of the right hip showed the defect to be slowly filling.

The patient had no abnormal neurologic symptoms following the operation. When seen fifteen months after the operation he presented no abnormal neurologic signs. There was

no apparent muscular weakness, but he stated that if he carried a heavy load slight limp developed. Walking caused him no inconvenience, but he was unable to run well. The grafted area in the skull was firm.

## COMMENT

It is to be emphasized that a large graft may be obtained from the ilium to cover an extensive cranial defect. The average surface available for a graft from the external table is approximately 14 to 15 by 9 to 12 cm.; that available from the table is 11 to 13.5 by 8 to 10 cm. An obvious objection is that a spontaneous fracture may develop in the ilium after the graft has been removed. In the case of a large graft there may be a limp lasting for several months as a result of weakness of the gluteal muscle. Another disadvantage is the fact that two surgical teams are necessary to carry out the two major procedures that must be performed. That the cosmetic result is superior to that obtained with the use of bone from ribs, the tibia or other more accessible parts is indisputable. However, it is no better than that which may be obtained with the use of nonosseous substances. The desirability of such a herculean procedure will depend on the ultimate fate of the graft and the relative likelihood of infection if an osseous or a nonosseous graft is used.

It is generally agreed (Naffziger<sup>11</sup>; Kolodny<sup>11</sup>) that osseous transplants are eventually absorbed and that only a dense fibrous sheet is left. This layer may be sufficient to maintain the normal contour of the skull and give a good cosmetic result. Yet little protection is afforded by such a fibrous sheet of tissue. Nonosseous grafts have the disadvantage that they usually cause a certain amount of tissue reaction which may predispose to infection. If, however, a nonosseous substance could be used that would not irritate the tissues unduly, it would have the advantages of durability and ease of application, which are not possessed by osseous grafts. Vitallium<sup>2</sup> and tantalum have been suggested as such substances.

Walker, Taggart and Lambros<sup>3</sup> in this clinic have been using a plastic which can be readily molded to the desired shape and size (methyl methacrylate<sup>4</sup>). It evokes minimal reaction from the tissues, so that little fluid collects under the cutaneous flap. This plastic may be used at the primary operation or inserted later.

The plastic insert is prepared in the desired thickness and size and perforated every 2 cm. with a 5 mm. drill. With the aid of heat it is molded over a plaster moulage of the patient's head. While tightly bandaged on the moulage, it is sterilized in the autoclave. The plate, slightly larger than the defect, is held in place by silk sutures placed through the margin of the bone. The dura is sutured to the under surface of the scalp through the holes in the plastic. This allows approximation of the dura and the scalp, thus obliterating a dead space. Occasionally the dura mater cannot be so elevated, but the result may still be satisfactory. The scalp wound is closed without drainage. Aspiration of the wound is rarely necessary when this plastic is used.

## SUMMARY

One case is reported, in which a large defect of the skull was repaired by a graft from the ilium. The technic of this procedure is given in detail. Nonosseous substances, such as an inert plastic, for repairing cranial defects would be desirable if the tissue reaction were minimal.

2. Peyton, W. T., and Hall, H. B.: *The Repair of a Cranial Defect with a Vitallium Plate*, *Surgery* 10:711, 1941.

3. Walker, A. E.; Taggart, J. K., Jr., and Lambros, V. S.: Unpublished data.

4. Methyl methacrylate is manufactured by Fricke and Getz Dental Manufacturing Company, Chicago, under the trade name of Vitacrilic and by E. I. Du Pont de Nemours & Company, New York, under the trade name of Lucite.

# AN EVALUATION OF THE BLOOD TEST FOR GALACTOSE TOLERANCE IN THE DIAGNOSIS OF HYPERTHYROIDISM

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Several reports have appeared in the literature concerning the experience of various workers with the blood test for galactose tolerance first described by Althausen and Wever in 1937.<sup>1</sup> We<sup>2</sup> have found the test to be a valuable adjunct in the diagnosis of hyperthyroidism, and it seems pertinent at this time to summarize and evaluate the results reported to date and to present our additional experience with the test.

Hirose,<sup>3</sup> utilizing the test for galactosuria introduced by Bauer<sup>4</sup> in 1906, was the first to demonstrate an impairment of galactose tolerance in thyrotoxicosis. Rowe,<sup>5</sup> using a modification of Bauer's test, found impaired tolerance to galactose in hyperthyroidism, hyperpituitarism, adrenal disease, ovarian and pancreatic failure and hepatic disease. Increased tolerance was noted in hypothyroidism and hypopituitarism. Rowe stressed the complex factors affecting galactose metabolism in the human economy and believed that the tolerance as measured with his technic represented the algebraic sum of several reinforcing and antagonistic agencies.

The description of a method for the quantitative determination of galactose in blood by Raymond and Blanco<sup>6</sup> in 1928 provided the impetus for the clinical investigation of galactose tolerance by means of blood tests. Harding and Grant<sup>7</sup> administered 40 Gm. of galactose to 16 normal male subjects and concluded that the peak of the concentration of galactose in the blood was usually not more than

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From the Laboratories and Wards of the Mount Sinai Hospital.

1. Althausen, T. L., and Wever, G. K.: Galactose Tolerance in Hyperthyroidism, *J. Clin. Investigation* **16**:257-259 (March) 1937.

2. Meranze, D. R.; Likoff, W. B., and Schineeborg, N. G.: The Blood Galactose Tolerance Test, *Am. J. Clin. Path.* **12**:261-271 (May) 1942.

3. Hirose, M.: Ueber die alimentäre Galaktosurie bei Leberkrankheiten und Neurosen, *Deutsche med. Wchnschr.* **38**:1414, 1912; cited by MacLagan.<sup>13</sup>

4. Bauer, R.: Weitere Untersuchungen über alimentäre Galaktosurie, *Wien. med. Wchnschr.* **56**:2537-2545, 1906; cited by Rowe and McManus.<sup>5e</sup>

5. (a) Rowe, A. W.: Metabolism of Galactose: Threshold of Tolerance in Normal Adults, *Arch. Int. Med.* **34**:388-401 (Sept.) 1924; (b) Metabolism of Galactose: Influence of Disturbed Endocrine Function, *Am. J. M. Sc.* **190**:686-700 (Nov.) 1935; (c) Metabolism of Galactose: Influence on Tolerance of Coexisting Endocrinopathies, *ibid.* **190**:701-708 (Nov.) 1935. (d) Rowe, A. W., and McGuiness, M.: Metabolism of Galactose: Effect on Tolerance of Level of Ovarian Activity, *Am. J. Obst. & Gynec.* **16**:687-698 (Nov.) 1928. (e) Rowe, A. W., and McManus, M.: Metabolism of Galactose: Influence of Hepatic Dysfunction on Tolerance, *Am. J. M. Sc.* **181**:777-788 (June) 1931.

6. Raymond, A. L., and Blanco, J. G.: Blood Sugar Determination and Separation of Sugars with Live Yeast, *J. Biol. Chem.* **80**:631-642 (Dec.) 1928.

7. Harding, V. J., and Grant, G. A.: The Metabolism of Galactose, *J. Biol. Chem.* **99**:629-646 (Jan.) 1933.

30 mg. per hundred cubic centimeters but occasionally increased to 60 mg. Althausen and his associates<sup>8</sup> first applied the blood test for galactose tolerance to the study of hyperthyroidism, and the technic they described has been followed, with slight modifications, by subsequent workers. They considered a concentration of 10 to 30 mg. per hundred cubic centimeters of blood normal after the oral administration of 40 Gm. of galactose. Values below 10 mg. represented increased tolerance and over 30 mg. depressed tolerance; the 30 to 40 mg. range was found to represent values of doubtful interpretation. One hundred and twenty-four hyperthyroid patients so tested revealed depressed tolerance; in 5 patients the tests gave doubtful results, and in 1 the result was normal. Hepatic insufficiency and Paget's disease were presented as the only two clinical conditions that might interfere with the test in the diagnosis of thyrotoxicosis, since both of these conditions produced consistent depressions in tolerance. On the basis of experimental work on animals<sup>9</sup> and the demonstration of normal tolerance to intravenously administered galactose in 10 patients with hyperthyroidism in whom oral administration had revealed the usual impaired tolerance,<sup>8a</sup> Althausen concluded that the absorption of galactose from the intestine was accelerated in thyrotoxic subjects. He suggested that the thyroid hormone influenced absorption of galactose mainly by accelerating its rate of phosphorylation. His advocacy of the blood test for galactose tolerance as an adequate clinical test of intestinal absorption<sup>10</sup> was followed shortly by the demonstration by Beams, Free and Glenn<sup>11</sup> of decreased intestinal absorption of galactose in patients with deficiency diseases, such as pellagra, nontropical sprue and rosacea keratitis. In England, MacLagan viewed the test as a means of estimating hepatic function<sup>12</sup> and found it useful in the differential diagnosis of jaundice<sup>13</sup> and in judging hepatic dysfunction in thyrotoxicosis.<sup>14</sup> Thirty of his 41 subjects with thyrotoxicosis revealed definite impairment in galactose tolerance, and the remaining 11 all had results above the normal average. MacLagan's criteria for normal and abnormal values differed widely from those noted by Althausen and by us, since his upper limit of normal was 80 mg. per hundred cubic centimeters. Variations in technic appear insufficient to account for the wide difference in the normal values obtained by the two groups. Wilson,<sup>15</sup> adhering to the technic and standards reported by MacLagan, found values above 40 mg. for 22 of 24 thyrotoxic patients; 1 patient had values in the 30 to 40 mg. range and 1 a peak of only 9 mg. Despite Wilson's adherence to MacLagan's standards, his values for subjects with hyperthyroidism closely paralleled those of Althausen and of other American workers. We<sup>2</sup> studied 162 subjects, 36 of whom were hyperthyroid. Only 1 of these revealed normal

8. (a) Althausen, T. L.; Lockhart, J. C., and Soley, M. H.: New Diagnostic Test (Galactose) for Thyroid Disease, *Am. J. M. Sc.* **199**:342-351 (March) 1940. (b) Althausen and Wever.<sup>1</sup>

9. Althausen, T. L., and Stockholm, M.: Influence of the Thyroid Gland on Absorption in the Digestive Tract, *Am. J. Physiol.* **123**:577-588 (Sept.) 1938.

10. Althausen, T. L.: A Test for Intestinal Absorption, *Am. J. Digest. Dis.* **6**:544-549 (Oct.) 1939.

11. Beams, A. J.; Free, A. H., and Glenn, P. M.: The Absorption of Galactose from the Gastro-Intestinal Tract in Deficiency Diseases, *Am. J. Digest. Dis.* **8**:415-421 (Nov.) 1941.

12. MacLagan, N. F.: Galactose Tolerance as a Test of Liver Function, *Quart. J. Med.* **9**:151-162 (April) 1940.

13. MacLagan, N. F.: Galactose Tolerance in Jaundice and Hyperthyroidism, *Proc. Roy. Soc. Med.* **34**:602-606 (July) 1941.

14. MacLagan, N. F.; Rundle, F. F.; Collard, H. B., and Mills, F. H.: Liver Function in Thyrotoxicosis, *Quart. J. Med.* **9**:215-228 (July) 1940.

15. Wilson, T. E.: The Galactose Tolerance Test in Thyrotoxicosis, *M. J. Australia* **1**:33-44 (Jan. 10) 1942.

galactose tolerance. However, because of the discovery of depressed galactose tolerance in a heterogeneous collection of disease entities, we stressed the value of normal results in excluding the diagnosis of hyperthyroidism rather than the value of abnormal results in establishing that diagnosis. Smith, Jondahl and Ochsner<sup>16</sup> found 1 normal test (doubtful zone) among 41 hyperthyroid patients studied. Of 20 persons with hyperthyroidism studied by Rosenkrantz, Bruger and Lockhart<sup>17</sup> normal tolerance was found in 1; they too pointed out various nonthyroid states associated with depressed galactose tolerance.

The detailed technic of the test has been described elsewhere.<sup>15</sup> Briefly, the concentration of galactose in samples of venous or capillary blood is determined thirty and sixty minutes after the oral administration of 40 Gm. of galactose to a patient who has fasted overnight. Galactose values are obtained by yeast fermentation of the dextrose in the blood and determination of the residual reducing substances. A fixed dose (40 Gm.) of galactose has been advocated<sup>5</sup> because it exceeds the capacity for intestinal absorption during the period of the test. The results obtained with doses of sugars varying with body weight or surface have proved disappointing from the standpoint of uniformity,<sup>7</sup> though some authors<sup>19</sup> have maintained that this method is more accurate. Repetition of the test on the same person revealed excellent uniformity of successive determinations.<sup>18</sup>

Galactose is absorbed by phosphorylation in the intestine without transformation and its absorption, within wide limits, is independent of its intestinal concentration and of gastric emptying time.<sup>10</sup> It is absent in the blood of normal fasting subjects,<sup>7</sup> is not utilized as galactose by the tissues but must be converted first to dextrose in the liver,<sup>15</sup> is uninfluenced by insulin,<sup>12a</sup> is a well utilized sugar when given in small amounts<sup>20</sup> and is not retained by any renal threshold.<sup>21</sup> The factor of age per se, investigated by Rosenkrantz, Bruger and Lockhart,<sup>17</sup> appeared to exert little influence on galactose tolerance.

Though Althausen established a definite range of values for tolerance tests in normal subjects,<sup>8</sup> an analysis of the results (table 1) obtained by other workers reveals a wider range of normal values in individual instances. Twenty-two (23.4 per cent) of the 94 normal persons individually tabulated had galactose values above 30 mg. per hundred cubic centimeters, and 6 (6.4 per cent) had values under 10 mg.

Since our first publication<sup>2</sup> we have performed additional tests, bringing the total number to 220 subjects, of whom 48 had definite clinical hyperthyroidism. Forty-five of these 48 subjects had values above 40 mg. per hundred cubic centimeters; 2 had values in the doubtful 30 to 40 mg. zone, and 1 had a normal concentration. The average of the peaks was 84.2 mg., with a range of 25.4 to 150 mg. The one normal result was obtained for a 40 year old woman whose basal metabolism was over + 30 per cent on two occasions and whose peak blood galactose value was 25.4 mg. She improved considerably after subtotal thyroid-

16. Smith, M. C.; Jondahl, W., and Ochsner, A.: The Significance of the Galactose Tolerance Test in Hyperthyroidism, *Surg., Gynec. & Obst.* **74**:1083-1086 (June) 1942.

17. Rosenkrantz, J. A.; Bruger, M., and Lockhart, A. J.: Studies on Galactose Tolerance with Especial Reference to Thyroid Disease, *Am. J. M. Sc.* **204**:36-41 (July) 1942.

18. Meranze, Likoff and Schneeberg.<sup>2</sup> Althausen, Lockhart and Soley.<sup>8</sup>

19. (a) Roe, J. H., and Schwartzman, A. S.: Galactose Tolerance of Normal and Diabetic Subjects, and Effect of Insulin upon Galactose Metabolism, *J. Biol. Chem.* **96**:717-735 (June) 1932. (b) Beams, Free and Glenn.<sup>11</sup>

20. Harding, V. J., and van Nostrand, F. H.: Variations in Blood and Urinary Sugar After Ingestion of Galactose, *J. Biol. Chem.* **85**:765-778 (Feb.) 1930.

21. Folin, O., and Berglund, H.: Transportation, Retention and Excretion of Carbohydrates, *J. Biol. Chem.* **51**:213-273 (March) 1922.



ectomy, and microscopic examination of the gland revealed moderate hyperplasia. Fifteen months later the test was repeated and revealed a galactose peak of 50.8 mg., though the patient was symptom free. Table 2 summarizes the results reported in the literature for 304 thyrotoxic patients and reveals positive results in 280 cases (92.1 per cent).

We have failed to confirm the reported prompt return to normal of the galactose tolerance of patients after thyroidectomy. Althausen<sup>8</sup> repeated the test "at the time of discharge from the hospital" for 22 patients and found that 18 (82 per cent) had returned to normal. Twelve of 16 patients so investigated by MacLagan<sup>11</sup>

TABLE 1.—*Values Reported by Various Authors for Galactose in the Blood of Normal Subjects*

	Number of Subjects				Range of Values, Mg. per 100 Cc.	
	Total	Below 10 Mg.	10-30 Mg.	30-40 Mg.		Over 40 Mg.
Althausen, Lockhart and Soley <sup>8</sup> ; Althausen <sup>10</sup> .....	21	..	20	1 (above 30)	13-31	
Hurdling and Grant <sup>7</sup> .....	16	4	7	2	3	8-70
MacLagan <sup>12</sup> .....	50 normal persons—individual results not stated					Up to 50
Wilson <sup>15</sup> .....	..	..	..	..	..	....
Meranze, Likoff and Schneeborg <sup>2</sup> .....	10	2	8	..	..	5-27
Smith, Jondahl and Ochsner <sup>16</sup> .....	10 normal persons—individual results not stated					9-41
Rosenkrantz, Bruger and Lockhart <sup>17</sup> .....	47*	..	31	16 (above 30)		2-92
Totals .....	91	6	66	22		

\* Twenty-four persons over 50 years of age and 23 persons under 50 years without evidence of hyperthyroidism, liver disease or nephritis.

TABLE 2.—*Reported Results in Thyrotoxic Patients*

	Number of Subjects					Range of Values, Mg. per 100 Cc.
	Total	Below Normal	Normal	Doubtful	High	
Althausen, Lockhart und Soley <sup>8</sup> .....	130	..	1	5	124	25-152
*MacLagan <sup>15</sup> ; MacLagan, Rundle, Collard and Mills <sup>14</sup> .....	41	..	11	(?)	30	.....
*Wilson <sup>15</sup> .....	21	1	..	1	22	9-136
Meranze, Likoff and Schneeborg <sup>2</sup> .....	48	..	1	2	45	25.4-150
Rosenkrantz, Bruger and Lockhart <sup>17</sup> .....	20	..	1	..	19	17-136
Smith, Jondahl and Ochsner <sup>16</sup> .....	41	..	..	2	40	.....
Totals.....	301	1	14	8	280	

\* Normal values of these authors are above the 10 to 30 mg. normal range of American workers.

showed a "striking decrease in . . . galactose values . . . two weeks postoperatively." Wilson<sup>15</sup> included 6 patients in his tabulated results on whom the test was performed "after subtotal thyroidectomy" but does not record the interval. The galactose peaks for 3 of these 6 patients were over 40 mg., and a fourth peak was 32 mg. We repeated the test on 18 patients with hyperthyroidism ten to fourteen days after subtotal thyroidectomy and found normal values in only 3 patients. In 12 of the 15 patients in whom depressed tolerance to galactose persisted the basal metabolic rate had returned to normal, and in the remaining 3 the metabolism had been appreciably reduced by the operation. In addition, the test was performed on 15 patients on whom thyroidectomy had been done one to eight years previously. We had not the opportunity to perform preoperative tests. Ten of the 15 subjects showed depressed galactose tolerance. Despite these findings, for only 1 of these 15 persons was a second thyroidectomy considered

necessary. This permanency of altered galactose tolerance in such a large percentage of patients makes the test, in our experience, unreliable as a diagnostic aid when a recurrence of thyrotoxicosis is suspected.

The test is found especially helpful in excluding the diagnosis of hyperthyroidism in those patients in whom hypermetabolism (basal metabolic rate over  $\pm 20$  per cent) and certain suggestive signs and symptoms of thyrotoxicosis coexist. In several such instances the implications of the normal galactose tolerance have been corroborated by further study and observation. Patient 1 was a woman three months pregnant with a basal metabolic rate of  $\pm 29$  per cent, a peak galactose of 11.1 mg. and clinical signs suggestive of hyperthyroidism. She failed to improve after subtotal thyroidectomy, and pathologic examination of the thyroid revealed a normal gland. Patient 2 had a small goiter, hypermetabolism and normal galactose tolerance. Operation was performed without benefit to the patient, and microscopic examination of the gland failed to reveal any evidence of thyroid hyperactivity. Patient 3, a 41 year old man with mild hypertension, was similarly thyroidectomized for suggestive toxic symptoms and signs and because of an elevated basal metabolic rate (plus 29 per cent). His blood galactose peak was 24.8 mg. When seen four months later he was clinically unimproved. One of us (D. R. M.) reported a "moderately colloid goiter." In 2 similar cases, surgical intervention was contemplated but was postponed when a period of rest in bed reduced the hypermetabolism and tachycardia to normal limits. Patients with severe hypertension frequently have elevated basal metabolic rates, readings of  $\pm 25$  per cent or higher not being uncommon.<sup>22</sup> In 5 such patients with normal galactose tolerance, hypermetabolism, provisionally ascribed to thyrotoxicosis, was found to be incidental to compensated hypertensive cardiovascular disease. In cases of various functional and psychogenic disorders hyperthyroidism is frequently suspected, and if hypermetabolism coexists the differential diagnosis becomes difficult. In 2 such instances, the implication of the normal results obtained in galactose tolerance tests was soon strengthened by the clinical course of the patients. Of 21 patients with various psychogenic disorders (anxiety neuroses, hysterias, etc.) 18 revealed normal galactose tolerance: the galactose peaks of the remaining 3 were 37.2, 48.9 and 91.7 mg.

Both MacLagan<sup>14</sup> and Wilson<sup>15</sup> found galactose tolerance relatively unaffected by iodine therapy and indicated the value of the test in diagnosing thyrotoxicosis in patients who were first seen with normal basal metabolic rates after a course of iodine therapy. Smith, Jondahl and Ochsner<sup>16</sup> noted, however, that when patients with hyperthyroidism showed a good clinical response to preoperative management and medication the galactose curve tended to approach normal, though not in direct proportion to the basal metabolic rate. We tested 5 hyperthyroid patients on the day before operation after iodine therapy. In 4 of these 5 patients high galactose values persisted. These results tend to substantiate the findings of MacLagan and Wilson.

Galactose peaks below 10 mg. were reported by Althausen<sup>5</sup> and by Smith<sup>16</sup> in myxedema and by Beams<sup>11</sup> in various deficiency diseases.

To insure the logical use of any laboratory test, the physician must be well informed concerning factors which may complicate the interpretation of the results of that test. Althausen<sup>5a</sup> believed that only advanced hepatic insufficiency and Paget's disease would interfere with the use of the galactose test for the diagnosis of hyperthyroidism. We<sup>2</sup> described abnormal galactose tolerance in a greater

22. Yater, W. M.: *The Fundamentals of Internal Medicine*, New York, D. Appleton-Century Co., Inc., 1938, p. 477.

variety of disease entities, and our subsequent experience has confirmed this observation. We too observed abnormal galactose tolerance in cases of advanced hepatic insufficiency. In all the 11 cases of hepatocellular jaundice investigated and in 3 cases of cirrhosis of the liver the tests gave positive results. The peak galactose level reached in our 1 case of Paget's disease was 31.6 mg. The combination of hypermetabolism, cardiac decompensation and certain signs suggestive of thyrotoxicosis frequently exists and may present a confusing diagnostic problem. The blood test for galactose tolerance, in our hands, has proved to be of no value in such instances. The following case is cited to illustrate this point:

L. L., a white man 54 years of age, was observed in March 1940 in decompensation secondary to hypertensive cardiovascular disease. He complained of nervousness and hyperhidrosis. Mild exophthalmos was present. His basal metabolic rate, on many observations, averaged +34 per cent. The peak of blood galactose was 47 mg. per hundred cubic centimeters, and the level of cholesterol in the blood, as determined by Bloor's test, was 172 mg. per hundred cubic centimeters. His basal metabolic rate remained high, and he failed to improve after treatment with iodine. In November 1940 the basal metabolic rate was +30 per cent and two galactose tests done seven days apart showed peaks of 45.8 and 80.1 mg. In November 1941 the galactose peak was 44 mg. The thyroid gland, obtained at autopsy in August 1942, was normal grossly and microscopically.

Blood galactose tolerance tests revealed depressed tolerance in 13 of 23 patients during mild cardiac decompensation; 4 patients had values in the doubtful zone, and 6 had normal values. In 7 of these 23 patients hypermetabolism was also present; 4 of the 7 in addition had depressed galactose tolerance. Of 8 patients hospitalized for active peptic ulcer, 5 had depressed tolerance to galactose, 1 had a value in the doubtful zone and 2 had normal values. In table 3 a great variety of heterogeneous disease entities in which various authors found depressed galactose tolerance are tabulated. Rosenkrantz, Bruger and Lockhart<sup>17</sup> mentioned Bright's disease, infections of the upper respiratory tract, impaired hepatic function, malignant disease and therapy with sulfonamide compounds as conditions very frequently producing impairment in galactose tolerance. We feel that when in cases of suspected hyperthyroidism the presence of hepatic insufficiency, cardiac decompensation, Paget's disease and peptic ulcer can be eliminated and a history of a previous thyroidectomy for hyperthyroidism is not obtained the impaired galactose tolerance is very likely due to thyrotoxicosis.

We have mentioned the two theories that have been offered to explain the mechanism of the test, (1) accelerated intestinal absorption<sup>23</sup> and (2) hepatic dysfunction.<sup>12</sup> Althausen short-circuited the gastrointestinal tract by intravenous administration of galactose and found normal values in the blood of 10 persons with hyperthyroidism who had had high blood values with the oral test. We retested 5 patients with hyperthyroidism by a technic described by Althausen<sup>24</sup> for intravenous administration of galactose, but in all 5 cases the galactose values were still appreciably elevated. As a control 5 intravenous tests were done on 5 normal subjects who on previous testing had shown normal tolerance for orally administered galactose. In all 5 subjects values were normal.

We were unable to find any correlation between the results of the bromsulphalein and/or the hippuric acid synthesis test and those of the blood galactose tolerance test in 45 patients so studied. Thus of 38 patients in this group who showed depressed tolerance to galactose, 20 had normal hepatic function and 18 had abnormal hepatic function as evaluated by these tests. Of the 7 patients with normal galactose tolerance in this group, 3 had normal hepatic function and 4 had

23. Althausen, Lockhart and Soley.<sup>8</sup> Althausen and Stockholm.<sup>9</sup> Althausen.<sup>10</sup>

24. Althausen, T. L.: Personal communication to the author.

abnormal function. Wilson,<sup>25</sup> too, was unable to demonstrate any correlation between tests of hepatic function and galactose tolerance. Lichtman<sup>25</sup> performed the urine galactose tolerance test on 13 patients with thyrotoxicosis and found that 6 of them (46 per cent) had abnormal excretion of galactose (3 to 12.5 Gm.), which he believed indicated hepatic dysfunction incident to thyrotoxicosis. Wilson<sup>25</sup> noted abnormal galactosuria in 8 of his 24 hyperthyroid patients (33

TABLE 3.—*Heterogeneous Diseases with Abnormal Galactose Tolerance*

Disease	Totals	Below 10 Mg.	Normal	Doubtful	High
Hepatocellular jaundice.....	51	..	..	..	51
Cirrhosis of the liver.....	6	..	..	..	6
Carcinoma of the liver.....	1	..	..	..	1
Hemochromatosis.....	1	..	..	..	1
Obstructive jaundice.....	25	..	17	1	10
Cholecystitis.....	3	..	1	..	2
Cardiac decompensation.....	21	..	15	4	14
Hypertensive cardiovascular disease.....	6	..	2	..	4
Rheumatic heart disease.....	3	..	2	..	1
Idiopathic tachycardia.....	1	..	..	1	..
Peptic ulcer.....	11	..	4	1	6
Intestinal hypermotility.....	5	1	3	..	1
Amebiasis.....	2	..	..	1	1
Tuberculous ileitis.....	1	..	..	..	1
Idiopathic diarrhea.....	1	..	..	..	1
Cushing's syndrome.....	5	1	3	..	1
Hyperinsulinism.....	4	..	2	1	1
Diabetes mellitus.....	27	7	25	2	3
Menopause.....	4	1	..	..	3
Psychogenic disorders.....	45	4	35	3	6
Paget's disease.....	19	..	4	..	15
Pott's disease.....	1	..	..	..	1
Dyschondroplasia.....	1	..	..	..	1
Milkman's syndrome.....	1	..	1	..	1
Osteosarcoma.....	2	..	1	1	2
Perniciou anemia.....	10	3	4	..	3
Pellagra.....	9	5	1	..	3
Nephritis.....	7	..	1	6 patients	"Average curve high"
Rosacea keratitis.....	4	2	..	1	1
Simple goiter, nontoxic adenoma, etc.....	25	5	14	3	3
Urticaria.....	1	..	..	..	1
Fever, origin unknown.....	2	..	..	..	2
Infection of upper respiratory tract.....	9	..	..	..	..
Pulmonary tuberculosis.....	3	..	..	1	2
Pneumonia (convalescent after therapy with sulfonamide compounds).....	2	..	..	..	2
Congenital syphilis with chronic mastitis.....	1	..	..	..	1
Bronchiectasis.....	1	..	..	..	1
Iodine poisoning.....	1	..	..	..	1
Dystonia musculorum deformans.....	1	..	..	..	1
Hypertrophied tonsils.....	1	..	..	..	1

per cent) so tested. We simultaneously measured levels of galactose in the blood and output of galactose in the urine of 25 patients with various diseases. For 15 of them there was a correlation between the result of the blood test and that of the urine test (i. e., an elevated blood galactose level with excess galactosuria) and 10 revealed a lack of correlation. Of the 6 thyrotoxic patients in this group,

25. Lichtman, S. S.: Liver Function in Hyperthyroidism, with Special Reference to the Galactose Tolerance Test, *Ann. Int. Med.* 14:1199-1215 (Jan.) 1941.

only 1 was found to have abnormal excretion of galactose (5.43 Gm. in five hours). The aforementioned experimental results cannot therefore be interpreted as supporting unequivocally either theory of the mechanism of the test.

#### SUMMARY AND CONCLUSIONS

Three hundred and four cases of thyrotoxicosis in which the blood galactose tolerance test was performed have been collected from the literature. Two hundred and eighty (92.1 per cent) of the tests yielded positive results.

The test is useful in excluding the presence of hyperthyroidism in patients with hypermetabolism due to causes other than hyperthyroidism.

The test is unreliable in the diagnosis of hyperthyroidism in patients in whom thyroidectomy has previously been required for hyperthyroidism, in patients with decompensated cardiac disease and in patients suffering with peptic ulcer, hepatic insufficiency or Paget's disease.

The fact that the result of the test may be positive in any one of the heterogeneous disease entities presented and is rarely negative in the presence of hyperthyroidism emphasizes the value of the test in excluding the diagnosis of hyperthyroidism rather than in establishing that diagnosis.

In instances in which an estimation of the basal metabolic rate cannot be performed, the blood galactose test may be substituted.

The mechanism of the altered galactose tolerance in hyperthyroidism does not appear to have been definitely established. Therefore we believe that Rowe's contention that galactose tolerance depends on a multiplicity of complex factors influencing galactose metabolism is the most fruitful concept thus far advanced in the interpretation of the test.

Miss Dorothy Bunting, record room librarian of the Mt. Sinai Hospital, cooperated in the preparation of this paper, and Miss Violet Parnes gave technical assistance.

Fifth and Reed Streets.

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## DR. ROBERT B. OSGOOD

The people of the United States are under great obligation to that small north-eastern corner of the country which is called New England. The men and institutions of New England have had an immeasurable influence on thought and progress in this land. In the field of medical education the contributions have been large. In the more recent past, continuing this New England tradition, Dr. Robert Bayley Osgood played no small part in the teaching of orthopedic surgery and in the training of young men for the practice of this branch of medicine.

Born in Salem, Mass., of sea-faring forebears, he decided as a youth to become a physician. After graduating from Amherst College in 1895, he entered the Harvard Medical School and received his doctorate in medicine in 1899. Good fortune led him to become a student house officer at the House of the Good Samaritan, where the treatment of the patients was largely orthopedic in nature. Here his skill and enthusiasm commended him to the visiting surgeons, particularly to Dr. Joel E. Goldthwait.

In 1899, after graduating from the Harvard Medical School and completing a surgical internship at the Massachusetts General Hospital, he became associated with Dr. Joel E. Goldthwait and Dr. Charles F. Painter in the relatively new specialty of orthopedic surgery. He became interested at this time in the recently discovered roentgen rays and, with Dr. Walter J. Dodd, studied their practical application to diseases of the bones and joints. He became assistant to the orthopedic clinic of the Carney Hospital and also to the Children's Hospital, in Boston. At the latter institution he served as roentgenologist until the pressure of his increasing practice forced him to relinquish this work.

When an orthopedic service was begun at the Massachusetts General Hospital, he resigned his other hospital appointments and became a visiting orthopedic surgeon at this clinic. Here, with his appointment as instructor in orthopedic surgery in the Harvard Medical School in 1913, came his first opportunity for teaching. During this period a large number of his contributions to medical literature were made. In 1903 he reported observations on a lesion of the epiphysis of the tibial tubercle, which has since come to bear his name. With Dr. Goldthwait he studied the pelvic articulations and demonstrated their relationship to disabilities of the low region of the back. Papers were published by him on such diverse subjects as foot strain (in connection with which he described an ingenious apparatus for measuring the strength of the supporting muscles of the feet), internal derangement of the knee joint, scoliosis, arthritis, the mobilization of stiffened joints and the transmission of the virus of poliomyelitis.

With the entry of the United States into World War I, Dr. Osgood volunteered for service. He was commissioned as major in the Medical Corps of the Army of the United States and was called into active service in May 1917. He played a notable role in the organization of orthopedic services for the care of wounded American soldiers in France, where he was for a time assigned to Base Hospital No. 5. Transferred to the Medical War Office in London, he assisted Sir Robert

Jones in the establishment of orthopedic hospitals in Great Britain. He was detailed to the headquarters of Medical and Surgical Consultants at Neufchateau, then to the Office of the Chief Surgeon of the A. E. F. at Tours. Later he served as orthopedic consultant to the Surgeon General's Office in Washington. His efforts here contributed greatly to improved splinting and transportation of the wounded. At the close of the war he was promoted to the rank of colonel in the Medical Reserve Corps.

On his return to civil life he was elected chief of the orthopedic service at the Massachusetts General Hospital in 1919. Here his unusual ability as organizer and head of a clinic were shown. The orthopedic service of the Massachusetts General Hospital under his leadership became an important center for both undergraduate and postgraduate teaching in orthopedic surgery. In 1922 he became professor of orthopedic surgery in the Harvard Medical School and chief of the orthopedic service of the Children's Hospital in Boston. In 1924 he was made John B. and Buckminster Brown professor of orthopedic surgery. It was in the period between 1922 and 1930 that he, with Dr. Nathaniel Allison, organized a postgraduate teaching service for orthopedic surgery in Boston which became internationally famous and which attracted students from all parts of North America.

In 1930 he resigned his professorship and became professor emeritus. Since giving up his teaching and hospital positions he has been no less active in striving to raise the standard of orthopedic practice and to improve medical care in general. As a member of the Physician's Committee on Medical Care he struggled against outmoded and unethical medical practices under a storm of official disapproval and saw the eventual adoption of a newer and fairer policy. As a member of the American Committee on Rheumatism he helped to organize and develop the American Rheumatism Association. His services have been often sought as a lecturer and his counsel welcomed on the boards of many civil and medical organizations. He is chairman of the Advisory Board of Orthopedic Surgeons to the Trustees of the Shriner's Hospitals for Crippled Children and a member of the Advisory Committee of the Services for Crippled Children of the Children's Bureau in Washington.

The eminent position which he has attained in medicine is attested by the many important honors which have come to him. He was president of the American Orthopedic Association in 1920-1921, president of the New England Surgical Society in 1928-1929 and president of the American Rheumatism Association in 1942-1943. Amherst College conferred on him the degree of Doctor of Science, *honoris causa*, in 1935. He has been elected an honorary member of the British, Italian, Scandinavian and Australian orthopedic associations and of the Royal Society of Medicine. He is a corresponding member of the Belgian Orthopaedic Association.

We who have been his pupils and associates remember him best as a great teacher. He is known in medical councils as an able executive and a wise counselor. In medical research his part has been chiefly that of giving helpful advice and encouragement, seeking no credit for himself. A man of sound scholarship, facile in voice and pen, of the highest ideals both for his personal life and his profession, generous to a fault, speaking evil of no man, he has wielded and continues to wield a great influence for good on the practice of orthopedic surgery in America.

T. C. K.

# SURGICAL APPROACHES TO THE EPIPHYSIAL CARTILAGES OF THE KNEE AND ANKLE JOINTS

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AND

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SAN FRANCISCO

Excision of an epiphysial cartilage for the arresting of growth is not a new surgical procedure. As early as 1873, such an operation was performed by Ollier<sup>1</sup> for the correction of deformities caused by unequal rates of growth in the bones of the forearm and the leg. He did not, however, advocate this procedure for the equalization of length of the leg.

In 1933, Phemister<sup>2</sup> published his paper on "Operative Arrestment of Longitudinal Growth of Bones in the Treatment of Deformities," in which he emphasized the value of this operation on the lower femoral and upper tibial epiphysial cartilages in treating unequal length of legs in growing children. Many surgeons, ourselves included, have adopted the method of Phemister because of its simplicity and because it is a generally applicable procedure for children during the period of growth. In performing the operation, however, we have not found the straight incisions used by Phemister entirely satisfactory for the purpose of adequate exposure of these epiphysial cartilages. With this in mind, we have carried out special dissections in the anatomic laboratories which have resulted in the development of surgical approaches giving adequate exposure. The purpose of this article is to describe and illustrate these approaches. In addition, a description of the surgical approaches to the epiphyses of the lower ends of the tibia and fibula have been included because they contribute a certain amount of growth to these two bones.

## EXPOSURE OF THE LOWER FEMORAL AND UPPER TIBIAL EPIPHYSIAL CARTILAGES

The knee is held by sand bags in about 30 degrees of flexion, since this position relaxes the hamstring muscles and the bony landmarks can be readily palpated. If the lower femoral and the upper tibial epiphysis are to be fused at one operation, they are exposed through long, curved incisions over the internal and the external aspect of the knee joint. If either the lower femoral or the upper tibial epiphysis is to be fused alone, then the upper or lower halves respectively of the incisions are employed (fig. 1 a and 1 b).

*Lateral Aspect of the Knee Joint.*—The landmarks and important anatomic structures on the outer aspect of the joint are: (1) the lateral condyle of the femur; (2) the head of the fibula; (3) the tractus iliotibialis; (4) the lateral intermuscular septum; (5) the tendon of the biceps femoris muscle and (6) the common peroneal nerve.

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1. Ollier, L.: *Traité des résections et des opérations conservatrices, qu'on peut pratiquer sur le système osseux*, Paris, G. Masson, 1888, vol. 2, pp. 440-445; 1891, vol. 3, pp. 473-479.

2. Phemister, D. B.: *Operative Arrestment of Longitudinal Growth of Bones in the Treatment of Deformities*, J. Bone & Joint Surg. 15:1-15, 1933.



In this region, the lateral condyle is the most prominent portion of the femur. It lies just above and in front of the head of the fibula. Over this prominence the tractus iliotibialis passes to its insertion into the upper margin of the lateral tuberosity of the tibia and into the head of the fibula. The tendon of the biceps muscle is also inserted into the head of the fibula. This insertion is bifurcated by the fibular collateral ligament, which joins the tip of the head of the fibula and the lateral condyle of the femur. Beneath this ligament lie the inferior lateral genicular vessels after passing beneath the plantaris muscle and the lateral head of the gastrocnemius. Between the tendon of the biceps muscle posteriorly and the tractus ilio-

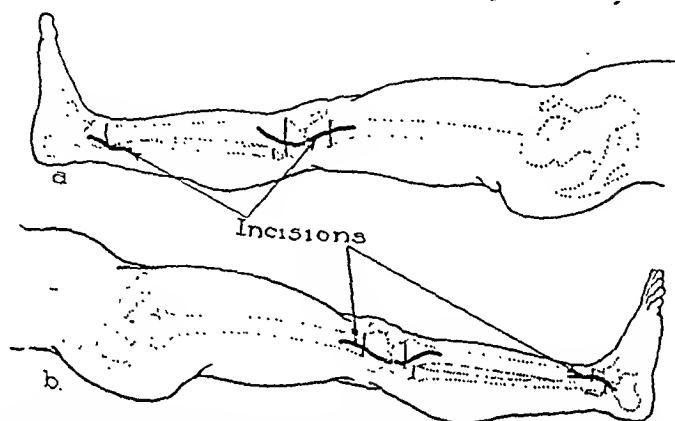


Fig. 1.—Sketches illustrating the lines of incision for the various approaches: *a*, the medial side of the leg; *b*, the lateral side of the leg.

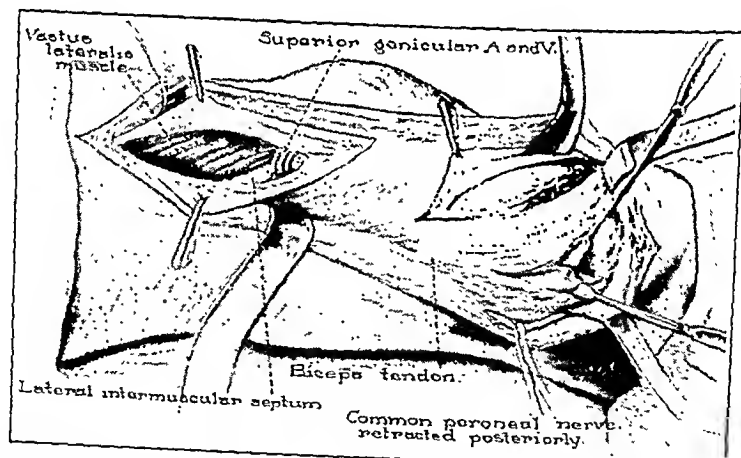


Fig. 2.—Combined approach to the lateral aspect of the knee for fusion of the lower femoral and upper tibial and fibular cartilage plates at one operation.

tibialis anteriorly, a distinct interval can be felt, in which is located the lateral intermuscular septum. The common peroneal nerve passes distally and laterally along the medial side of the biceps tendon. Below, it follows the interval between the tendon of the biceps femoris muscle and the lateral head of the gastrocnemius. Finally, it turns anteriorly around the neck of the fibula under cover of the proximal part of the origin of the peroneus longus muscle.

The incision in the skin begins about  $2\frac{1}{2}$  inches (6.4 cm.) above the lateral condyle of the femur directly over the interval between the biceps tendon and the tractus iliotibialis. It curves downward and backward to the head of the fibula

and then gently forward on the lateral surface of the upper part of the tibia (fig. 1*b*). The lateral intermuscular septum is exposed in the upper part of the wound and traced to its attachment to the linea aspera; this frees some of the fibers of origin of the vastus lateralis from its anterior surface (fig. 2). The muscle is retracted forward to expose the lateral surface of the femur and its junction with the lateral condyle. This junction marks the site of the epiphysial cartilage (figs. 3 and 4). Immediately below, the capsule of the knee joint should be identified. The superior lateral genicular vessels appear directly on the bone, passing forward after piercing the septum, and are distributed to the fibers of the vastus lateralis. For good

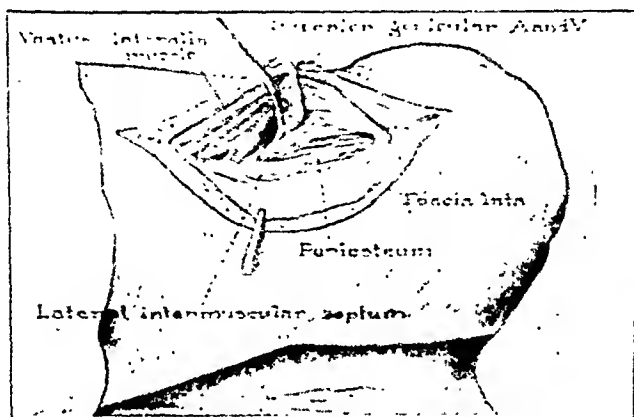


Fig. 3.—Detail of the approach to the lateral portion of the distal end of the femur.

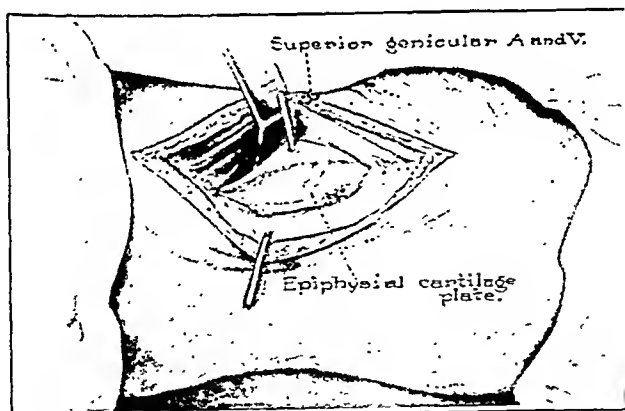


Fig. 4.—Detail of the approach to the cartilage plate at the lateral portion of the distal end of the femur after the periosteum has been elevated. The removal of a thin flake of bone by means of a sharp chisel will expose the cartilage plate.

exposure of the epiphysial line, they may require ligation. The periosteum is incised vertically, and a thin section of bone from the outer cortex is removed with an osteotome directly over the epiphysial line. The periosteum is then separated laterally, and a rectangular block of bone 2 cm. long and 1 cm. wide is removed. reversed and reinserted. Before this block of bone is replaced, however, the cartilage of the epiphysial line is removed with a curet to the depth of 1 cm. over as large a portion of the lateral circumference of the femur as can be reached. Subsequently, small shavings of bone are packed into the defect left in the cartilage plate, after which the rectangular block of bone is replaced (fig. 5).

The exposure of the upper fibular and tibial epiphysial cartilage is rendered safe by dissection of the common peroneal nerve. This structure is found by incision of the deep fascia directly posterior and internal to the tendon of the biceps muscle. From here it can be traced downward, freed at the neck of the fibula and retracted posteriorly (fig. 2). An incision over the upper and medial portions of the head of the fibula readily exposes its epiphysial cartilage; this is completely excised with an osteotome and the cavity then filled with thin shavings of bone. The cartilage plate of the tibia is revealed by downward reflection with a periosteal elevator of the upper fibers of origin of the extensor muscles from the arcuate line. The line of cartilage is shown by the removal of a thin section of bone  $\frac{1}{2}$  to  $\frac{3}{4}$  inch (1.3 to 1.9 cm.) below the margin of the joint. It is fused by the rectangular block method previously described.

*Medial Aspect of the Knee Joint.*—The anatomic structures with which we are concerned on the inner aspect of the joint are: (1) the adductor tubercle of the femur; (2) the medial intermuscular septum; (3) the inner hamstring muscles.

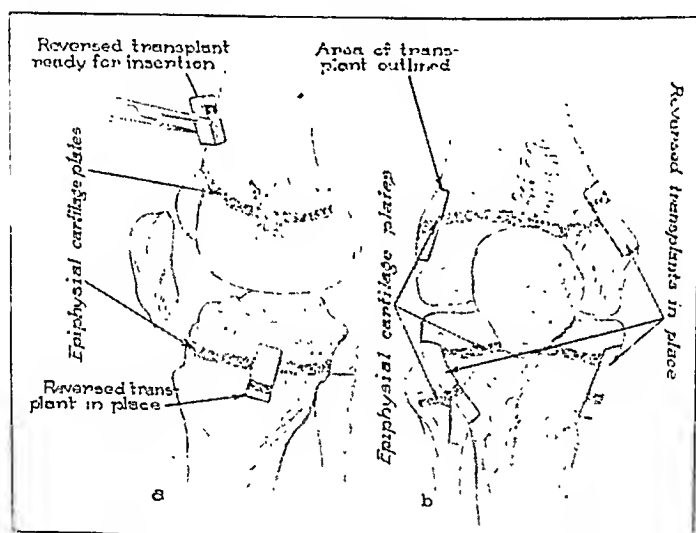


Fig. 5.—Diagram illustrating the details of the operative fusion of the epiphysial cartilages about the knee (drawn from Phemister<sup>2</sup>).

The adductor tubercle marks the junction of the epiphysis and diaphysis on the inner surface of the lower end of the femur. Into this prominent part of the bone the tendon of the adductor magnus muscle is inserted, and from it arises the superficial portion of the tibial collateral ligament. In addition, the joint capsule crosses the epiphysial cartilage at this level with the reflection of the synovial membrane just beneath it. Immediately proximal to the attachment of the joint capsule, the superior internal genicular vessels lie close to the bone, passing forward from the popliteal artery beneath the tendon of the adductor magnus.

The medial intermuscular septum is a much thinner membrane than the lateral intermuscular septum. It passes posteriorly from the general fascial envelope to its attachment with the linea aspera. This structure separates the adductor magnus muscle, behind, from the vastus medialis, in front, and it is in the interval between these two muscles that the epiphysial cartilage is readily exposed (fig. 6). The sartorius, gracilis and semitendinosus muscles pass over the tibial collateral ligament in the order named and from before backward to achieve insertion into

the upper, inner surface of the tibia. The infrapatellar branch of the saphenous nerve pierces the tendon of the sartorius muscle and turns forward to lie about  $\frac{3}{4}$  inch (1.9 cm.) below the upper margin of the tibia. Here, this branch can be rolled beneath the fingers.

An incision 5 inches (13 cm.) in length is made with its center approximately at the level of the adductor tubercle. In its upper part it passes over the inner surface of the internal condyle of the femur, and in the lower part it curves gently forward to follow the anterior margin of the tendon of the sartorius (figs. 1 and 6). By incision of the deep fascia the anterior surface of the internal intermuscular septum is identified and traced to its attachment to the linea aspera. The vastus medialis, after separation of a few fibers of origin from the septum, is retracted anteriorly, exposing an interval the floor of which is the internal surface of the femur and its junction with the flare of the adductor tubercle (fig. 6). The anterior and the posterior wall of this space are formed respectively by the vastus medialis muscle and the tendinous portion of the adductor magnus. In the distal

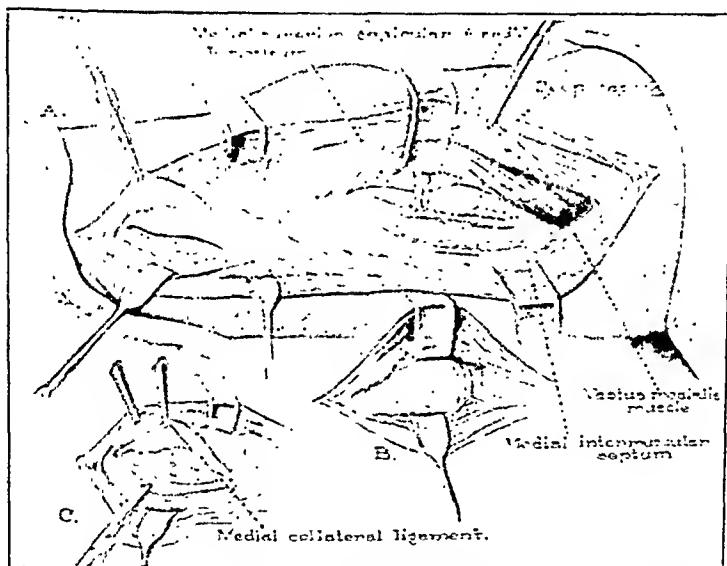


Fig. 6.—Combined approach to the medial aspect of the knee for fusion of the lower femoral and upper tibial cartilage plates at one operation.

portion of this space lies the epiphysial cartilage, overlapped by the attachment of the capsule and the reflected synovial membrane of the knee joint (fig. 6). The genicular vessels are ligated, and a vertical incision is made through the periosteum downward toward the epiphysial cartilage plate. The periosteum with the margin of joint capsule is pushed downward and laterally to expose the epiphysial cartilage. This exposure is facilitated by raising a portion of cortical bone. Fusion is carried out in the manner previously outlined.

The upper tibial epiphysis is now exposed by incising the deep fascia along the anterior margin of the sartorius tendon. The infrapatellar branch of the saphenous nerve lies forward and need not be exposed. In the depth of the wound the anterior margin of the tibial collateral ligament is found and retracted backward. The epiphysial cartilage is located directly in front of this ligament and  $\frac{1}{2}$  to  $\frac{3}{4}$  inch (1.3 to 1.9 cm.) below the upper margin of the tibia. It is exposed and fused in the usual manner.

# EXPOSURE OF THE EPIPHYSIAL CARTILAGES OF THE LOWER ENDS OF THE TIBIA AND FIBULA

For exposure of the epiphysial cartilages of the lower end of the fibula and the lateral aspects of the lower end of the tibia, an outward incision is made at the tip of the fibula and extended upward along the anterior margin of this bone for a distance of  $2\frac{1}{2}$  inches (6.4 cm.) (fig. 1 *b*). The anterior ligament of the

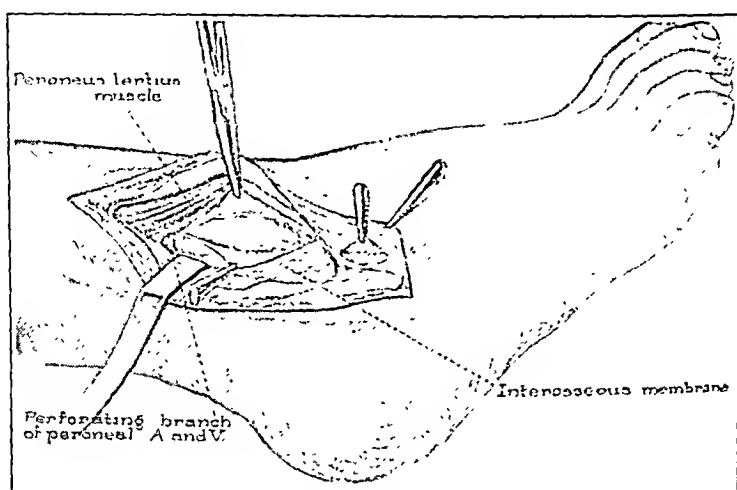


Fig. 7.—The approach to the lateral portion of the epiphysial cartilage of the lower end of the tibia and the epiphysial cartilage of the lower end of the fibula.

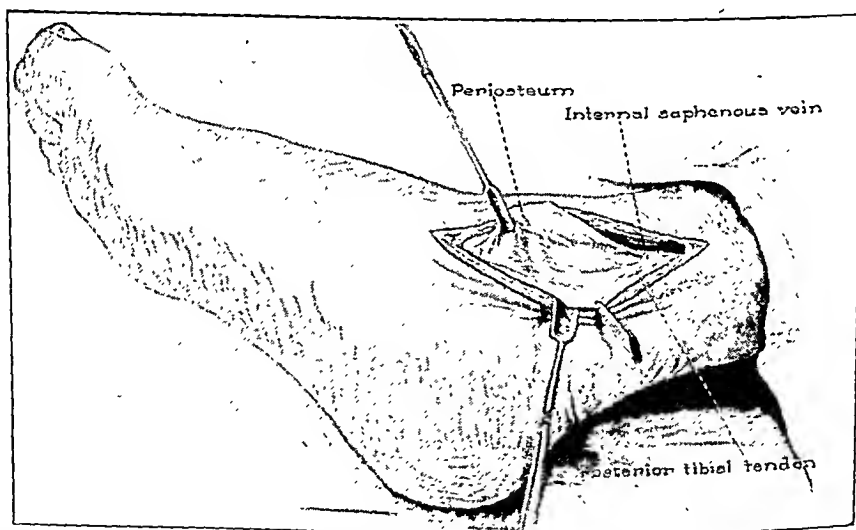


Fig. 8.—The approach to the medial aspect of the epiphysial cartilage of the lower end of the tibia.

lateral malleolus is identified and the deep fascia incised upward for about  $1\frac{1}{2}$  inches (3.9 cm.) above its upper margin. The peroneus tertius muscle is then retracted forward from its origin in the lower part of the fibula and the adjacent portion of the interosseous membrane (fig. 7). The perforating branches of the peroneal artery are seen lying on the interosseous membrane and may be either retracted or ligated as conditions warrant. From just above the attachment of the joint capsule, a vertical incision is made over the epiphysial cartilage of the

tibia, which in this location is about  $1\frac{1}{2}$  inch (1.3 cm.) above the margin of the ankle joint. The periosteum is reflected laterally while the epiphysial cartilage is exposed and insed. About  $1\frac{1}{2}$  inch above the tip of the fibula, the epiphysial cartilage of this bone is exposed and completely excised. The defect is then filled with bone chips.

On the medial aspect of the tibia, the skin incision, about 2 inches (5 cm.) in length, is made along the posterior margin of the tibia and internal malleolus (fig. 1). The saphenous vein lies anteriorly to this incision, while the flattened tendon of the tibialis posticus muscle forms a groove on the posterior part of the medial malleolus (fig. 8). The epiphysial cartilage lies about  $\frac{3}{4}$  to 1 inch (1.9 to 2.5 cm.) above the tip of the medial malleolus. It is brought into view by the elevation of the periosteum and the removal of a thin layer of bone. Care should be taken to curet the epiphysial cartilage well down over the posterior aspect of the tibia.

All of the wounds are closed by approximation of the deep fascia and the skin with interrupted silk sutures. Dressings are applied, and immobilization by splints or plaster is not necessary.

#### CONCLUSIONS

Surgical approaches to the epiphysial cartilages of the lower end of the femur and the upper and lower ends of the tibia and fibula are described in this paper. We have found that these approaches give adequate exposure for fusion of the cartilages and also permit due regard for the preservation of anatomic structures.

Dr. John Saunders, Professor of Anatomy, University of California, provided the facilities for the anatomic dissections.

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# DISLOCATION OF THE KNEE

## REPORT OF FOUR CASES

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Complete dislocation of the knee is relatively rare. Robbins<sup>1</sup> stated that up to 1909 only 270 cases had been reported in the literature, of which 114 were of the forward or anterior type of complete dislocation. Ritter<sup>2</sup> reported that complete dislocation of the knee was observed in only 1 of 23,000 patients admitted to the Reconstruction Hospital in New York. Ransohoff<sup>3</sup> stated that at the Cincinnati General Hospital only 3 persons with complete dislocation of the knee had been encountered in a period of twenty-eight years—1 had posterior and lateral dislocation, 1 anterior and lateral dislocation and 1 incomplete lateral dislocation.

As is well known, there are five types of dislocation: (a) anterior, (b) posterior, (c) medial, (d) lateral and (e) rotary. These are named according to the ways in which the tibia is displaced on the femur.

There is always considerable tearing of the lateral and cruciate ligaments in dislocation of the knee. The more complete the dislocation, the more complete is the tear.

## COMPLICATIONS

The popliteal vessels are torn occasionally, resulting in gangrene and loss of the leg. A case has been reported by me<sup>4</sup> in which there was a rupture of the popliteal artery and vein, resulting in gangrene. Robbins quoted Herring's experience of 6 miners who were caught in a shaft; 3 had forward dislocation, and in 2 cases amputation was necessary because of gangrene following injury of the popliteal vessels. He also quoted Hardouin, who found that in a series of 27 cases of posterior dislocation it was necessary to do 12 amputations because of injury to blood vessels. Ferguson and Allen<sup>4a</sup> reported a case in which thrombosis of the posterior tibial artery necessitated amputation of the leg thirty-five days after the initial injury.

Case 4 in the present series of 4 cases is another example of injury to the vessels following dislocation.

Neural complications have been reported by several authors. Mitchell<sup>5</sup> reported a case of anterior dislocation with peroneal paralysis, in which recovery was not complete. In a case of thrombosis of the posterior tibial vessel reported by Ferguson and Allen a complete division of the common peroneal nerve was shown. Patter-

1. Robbins, F. R.: Forward Dislocation of the Knee, *Ann. Surg.* 95:306 (Feb.) 1932.
2. Ritter, H. H.: Dislocation of the Knee Joint, with Report of a Case, *J. Bone & Joint Surg.* 14:391-394 (April) 1932.
3. Ransohoff, J.: Dislocations of the Knee, *Tr. West. S. A.*, December 1915, p. 81.
4. Anderson, R. L.: Dislocation of the Knee with Rupture of the Popliteal Artery and Vein: Report of Case, *Virginia M. Monthly* 58:120-123 (May) 1931.
- 4a. Ferguson, J. A., and Allen, L.: Complete Medial Dislocation of the Knee Joint with Division of the Common Peroneal Nerve, *J. Bone & Joint Surg.* 21:1012-1014 (Oct.) 1939.
5. Mitchell, J. I.: Dislocation of the Knee: Report of Four Cases, *J. Bone & Joint Surg.* 12:640-646 (July) 1930.

son<sup>6</sup> reported a case in which there was mild residual foot drop following dislocation of the knee.

Case 1 in the present series illustrates another complication, i. e., the necessity of open reduction, which may occur infrequently. Ruppanner<sup>7</sup> quoted Pagenstecher's review of 8 cases in the literature in which an operation was necessary for reduction. Ruppanner also reported a case in which a tibia in incomplete posterior and lateral dislocation was replaced by open reduction.

A frequent complication is one or more concomitant fractures, such as a fracture of the tibial spine or of the head of the fibula, and these usually require no special treatment.

The treatment consists of gentle reduction, usually by traction and pressure and counterpressure on the tibia and the femur with the patient under general anesthesia. It is agreed by all that after reduction a plaster cylinder should be used. There is some disagreement as to the length of time during which the complete plaster cylinder should be used. There is no general agreement as to how long the knee should be protected otherwise. Key and Conwell<sup>8a</sup> and also Conwell and Alldredge<sup>8b</sup> have advocated the use of a plaster cast for at least eight to twelve weeks. This is followed, if necessary, by a knee cage. Ritter reported a case, however, in which the cast was worn for only ten days, and then a walking caliper was applied, which was worn for five months with a good result. Longeway and Richardson<sup>9</sup> reported a case in which the cast was removed after fifteen days and a posterior splint applied, and later a hinged splint. Huber, Yaffe and Podlasky<sup>10</sup> and Wilson, Michele and Jacobson<sup>11</sup> cited cases in which there was a shorter time of immobilization with good results. Weigel<sup>12</sup> reported a case of anterior dislocation in which the knee was immobilized for five weeks. After two weeks the cast was bivalved for baking and massage. The patient began to bear weight after six weeks, and after eight weeks he was walking without crutches or cane. There was complete stability after three months. Weigel expressed the opinion that the result was due to good muscular development with exercises. Platt,<sup>13</sup> on the other hand, reported a case in which the cast was worn for four months.

Most authors feel that conservative treatment should be used first. Wilson, Michele and Jacobson stated that no operative treatment for the repair of ligaments should be used for at least two years. On the other hand, Hey Groves<sup>14</sup> recommended operative treatment for repair of the ligaments. There is no question about the tearing of the ligaments. The only question involved is whether or not the ligaments will heal sufficiently with protective treatment to function adequately.

6. Patterson, R. H.: Anterior Dislocation of the Knee Joint, *Ann. Surg.* 99:521 (March) 1934.

7. Ruppanner, E.: Zur Kenntnis der irreponiblen Kniegelenksluxationen, *Deutsche Ztschr. f. Chir.* 83:554, 1906.

8. (a) Key, J. A., and Conwell H. E.: *Fractures, Dislocations and Sprains*, ed. 2, St. Louis. C. V. Mosby Company, 1937, p. 1024. (b) Conwell, H. E., and Alldredge, R. H.: Complete Dislocations of the Knee Joint: A Report of Seven Cases with End-Results, *Surg., Gynec. & Obst.* 64:94-101 (Jan.) 1937.

9. Longeway, A. F., and Richardson, R. B.: Report of a Case of Complete Traumatic Dislocation of the Knee Joint Without Compounding, *Journal-Lancet* 51:120-122 (Feb.) 1931.

10. Huber, H. H.; Yaffe, A., and Podlasky, H. B.: Traumatic Dislocation of the Knee Joint: Report of a Case, *Radiology* 7:431-435 (Nov.) 1926.

11. Wilson, M. J.; Michele, A. A., and Jacobson, E. W.: Complete Dislocation of the Knee Joint, *Am. J. Surg.* 52:77-81 (April) 1941.

12. Weigel, E. W.: Complete Dislocation of Knee, *Am. J. Surg.* 9:140-141 (July) 1930.

13. Platt, H.: Traumatic Dislocation of the Knee Joint, *Brit. J. Surg.* 8:190-192 (Oct.) 1920.

14. Hey Groves, cited by Huber, Yaffe and Podlasky.<sup>10</sup>



## REPORT OF CASES

CASE 1.—A white man 52 years of age sustained an injury to his right knee on Jan. 7, 1942 when he was struck on a railroad trestle and knocked to the ground about 30 feet (9 meters) below. He was brought immediately to the McMillan Hospital in Charleston, where he complained chiefly of pain in the right knee.

Examination revealed that the tibia was displaced laterally on the femur (fig. 1 *A*). On the medial aspect of the knee over the medial condyle of the femur the skin was drawn taut and was at first cyanotic and later blanched. Just below this point there was a distinct dimple in the skin, corresponding to the line of the joint. Roentgen examination showed incomplete

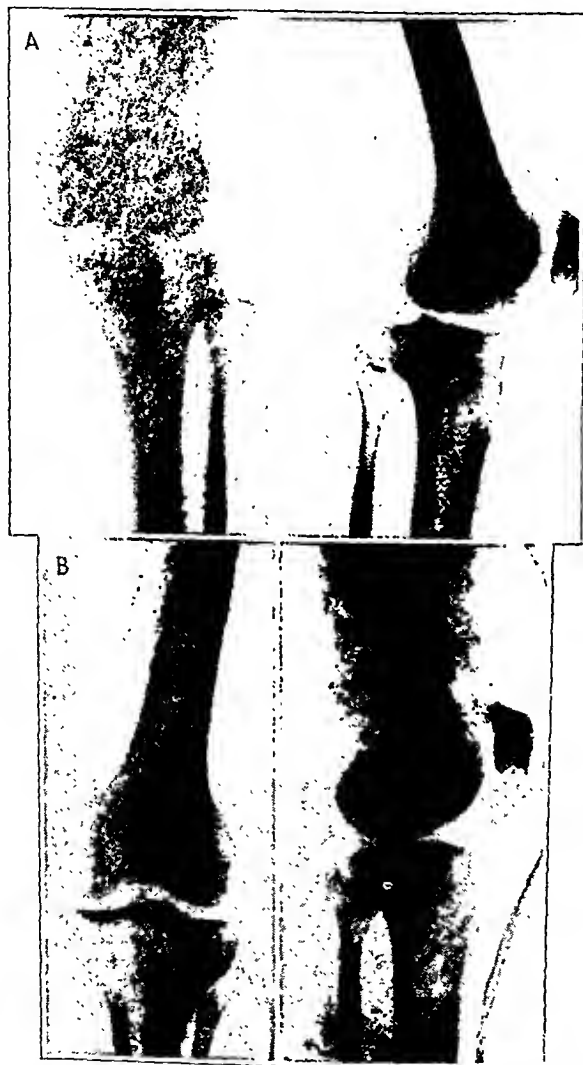


Fig. 1 (case 1).—*A*, roentgen films taken before reduction of incomplete lateral dislocation of the tibia on the right femur. *B*, after reduction.

lateral dislocation of the knee. With the patient under general anesthesia, an effort was made to reduce this deformity by manipulation both by my associate and by me, but it was unsuccessful.

We believed that this deformity had to be reduced promptly, as the circulation of the skin over the medial condyle of the tibia was poor.

Open reduction was performed. A  $2\frac{1}{2}$  inch (6.5 cm.) incision was made longitudinally over the median side of the knee. A small incision was made in the capsule of the joint, and a portion of the capsule on the medial side was found tucked under the femoral condyle. This was released with little difficulty by means of a Kelly clamp, and reduction was immediate and complete. This was confirmed by subsequent roentgen examination. The capsule and the skin were resutured, and a plaster cast was applied.

Convalescence was uneventful, and on the twenty-first day after his admission to the hospital the patient left, wearing a plaster cast. Two months later the cast was bivalved, and exercises were begun for the quadriceps muscle group, the anterior portion of the cast being removed. Two and one-half months afterward a hinged cast was applied.

Four months after the injury he still had considerable relaxation of the internal lateral ligament. A new hinged cast was applied. Subsequent examinations have shown gradual decrease in this relaxation, and the patient now walks without any support, showing slight relaxation in the internal lateral ligament and good motion in flexion.

**CASE 2.**—A Negro woman 55 years of age slipped and fell on Sept. 3, 1941, twisting her knee, while passing from one room to another in her work as a maid. When she was first seen, this woman of 250 pounds (113.5 Kg.) was lying in a corner near the door. She was placed on a stretcher with difficulty and taken immediately to the Charleston General Hospital.

Examination showed the right tibia to be displaced anteriorly and medially. There was marked swelling of the knee. The circulation and the nerves were intact.

Roentgen examination showed complete anterior and incomplete medial dislocation of the right knee. There was also a fracture of the head of the right fibula.

With the patient under general anesthesia, the dislocation was reduced by manipulation without difficulty. The postreduction roentgen film showed complete reduction.

The ligamentous relaxation was extreme, and the plastic cylinder was applied with unusual care to prevent redislocation.

She left the hospital on the following day. The circulation was good. She remained in bed for two weeks and then began to move about on crutches.

Eight weeks later there was marked evidence of relaxation of the internal lateral ligament, and there was still some relaxation of the anterior and posterior ligaments. Eight weeks after the injury the cast was bivalved, and measurements were taken for a long leg brace. One week later the brace was fitted, and motion was begun in the knee. Three months after the injury she began to bear weight. Six months after the injury she still had some relaxation of both lateral ligaments, especially the external lateral ligament, and some relaxation of both cruciate ligaments. However, this was decreasing steadily. Flexion of the knee was only slightly impaired at this time. It was believed that she was gaining a satisfactory result, although it will probably take another six months, with protection of the knee by a brace, for her to have a stable knee.

**CASE 3.**—A white woman 32 years of age was struck by an automobile on April 26, 1942, and the wheel of the automobile was said to have run over her left knee. She complained of pain in this knee. Examination on entrance showed complete anterior dislocation of the tibia on the femur. Unfortunately, a roentgen film was not taken before manipulation. Reduction was very easy by traction and manipulation. The roentgen film taken after reduction showed a fracture of the tibial spine and one of the head of the fibula in addition to the anterior dislocation. There was considerable swelling, and a metal splint was applied, which was changed to a plaster cast after four days. She left the hospital six days after the injury.

Six weeks and five days after the accident a hinged cast was applied, and motion of the knee was begun with bearing of weight. This cast was not comfortable, and three weeks later a brace was applied.

A little over five months after the accident she started leaving off the brace from time to time. Six months after the injury she was leaving off the brace more and more. At that time examination showed only slight relaxation of the anterior cruciate ligament, none in the posterior cruciate ligament, none in the internal lateral ligament and slight relaxation of the external lateral ligament. Flexion was present to 100 degrees. The musculature was in good condition, especially the quadriceps group.

She is still improving steadily, and an excellent result is anticipated. She does all of her own housework at this time and has no discomfort of the knee.

**CASE 4.**—A white man 76 years of age was injured at noon on June 17, 1942 when a horse kicked him and trampled on him. He was in the country and was not seen by us at the Kanawha Valley Hospital until three hours later. He was then in moderate shock. The left knee showed typical complete anterior dislocation of the tibia. The whole left lower leg was cold, and neither the pulse of the posterior tibial nor that of the dorsalis pedis artery was palpable. The roentgen films showed complete anterior dislocation of the tibia with a fracture of the head of the fibula and also marked calcification of the blood vessels. Unfortunately, these roentgen films have been misplaced.

General anesthesia was induced, and reduction was easy. A posterior splint was applied.

We were never able to palpate any pulse in the left foot, and the circulation remained greatly impaired. The whole leg became gangrenous up to the knee, and eleven days later, on



Fig. 2 (case 2).—*A*, lateral roentgen film taken before reduction of complete anterior and incomplete medial dislocation of the tibia on the right femur; *B*, after reduction. *C*, antero-posterior roentgen film taken before reduction; *D*, after reduction.

June 28, a guillotine amputation was performed in the lower part of the thigh. Traction was then applied after the usual method. The pathologic report was as follows.

"The dissection was performed twenty-four hours after amputation. The left leg was amputated about 10 cm. above the knee. All the toes and the anterior half of the foot showed blackish discoloration and were dry. The skin of the dorsum pedis was bluish. The subcutaneous tissue in the area of incision drained a large amount of brownish foul-smelling fluid. The skin of the lower part of the foot showed in some areas similar changes, especially on the lateral side. The margins of the amputation wound were irregular. On dissection the subcutaneous tissue of the whole leg showed blackish red discoloration. After dissection of the muscles the nerves and the blood vessels seemed to be embedded in blackish hemorrhagic tissue. Serial sections through the large blood vessels, including the popliteal artery and vein, showed extensive thrombosis completely obliterating the lumens of both arteries and veins. In the popliteal artery the thrombus showed a light brown color. There was an oblique fracture of the capitulum of the fibula.

"Sections from many areas of the popliteal and posterior tibial arteries were examined. The popliteal artery showed marked thickening of its intima and cholesterol deposits. In some areas the atheromatous content was emptied into the lumen and was visible within the thrombus. The



Fig. 3 (case 3).—Roentgen film taken after reduction of complete anterior dislocation of the tibia on the left femur, showing a fracture of the tibial spine and one of the head of the fibula.

media, beginning from the distal end of the popliteal artery downward, showed very extensive calcification. The lumens of all arteries and veins were occluded by thrombi.

"Diagnosis: Dislocation of the left knee; partly dry, partly moist gangrene of the foot and of the distal third of the lower leg; extensive thrombosis of all arteries and veins; extensive arteriosclerosis, mostly of the Mönckeberg type."

Immediately after the operation the patient began to improve, and with the aid of transfusions, made satisfactory progress. He left the hospital on July 22, 1942.

The stump granulated slowly and finally healed in four months. The poor general circulation undoubtedly contributed materially to this delay.

#### SUMMARY

Four cases are reported: (1) incomplete lateral dislocation for which open reduction was necessary; (2) complete anterior and incomplete medial dislocation; (3) complete anterior dislocation; (4) complete anterior dislocation followed by thrombosis of the popliteal vessels and gangrene.

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## KNOWING HOW TO LIVE

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To honor Dr. Robert Bayley Osgood is instinctive in all who know him, and to contribute to this volume is a privilege, for what orthopedic surgeon does not owe an everlasting debt of gratitude to this teacher and friend?

The title of this brief essay has been chosen with care, for "Dr. Bobby," as he is affectionately known to most of his students, is indeed an expert at the fine art of living.

As a young man, Dr. Osgood worked hard. He was a leading surgeon in World War I, and he labored unceasingly to build and perfect the orthopedic services at the Massachusetts General Hospital and the Children's Hospital. But fifteen years ago he began to exhibit a faculty often seen in men who are wise as well as great—the faculty of relaxation.

Relaxation is a gift, or rather an art, for while its roots are in the personality, perhaps in the endocrine apparatus, only with practice and studious application does one attain the ability to lock up the troubles of the day within an exit-proof compartment of the mind, and thus at the appointed time turn one's attention to some of the finer things of life.

Dr. Osgood has always been a man to whom family life has had a strong appeal. I still treasure our memories of his Sunday "open house," to which house officers of the Massachusetts General Hospital were frequently invited. The simple dignity of his home reflected a quality which is found in few men of this generation.

Relaxation in some persons might be taken for indolence, but there is never such a thought in reference to Dr. Osgood. His keenness of mind, his ability to make rapid decisions and his kindly but effective word of command leave no doubt as to his mental and physical activity. His interest in old books, so well shown in his splendid exhibit at the 1940 American academy of Orthopedic Surgeons, his appreciation of art and music—all these things have contributed to keep him young in spirit and healthy in body, and to make him really great.

Success cannot be measured by how much money a man makes, how fine a car he drives or how high his name appears in the social register, even though such things may seem important in these competitive days. But the man who enjoys life, who wears well, who really lives in the broader sense, is the one who takes time for his hobbies, his recreation and above all for definite relaxation. The average man says, "But I haven't time." That man is an egoist, for important as he may seem to be, no one can drop out of the mad race without finding his place filled by some one fully competent to carry on.

And this I should like to say to you, Dr. Osgood, in all seriousness: You have always been an outstanding figure in your chosen field of Orthopedic Surgery. But more than that, you have guided many minds and hands into the right pathways. Thus you have inspired and enlightened your successors. Thus the men you have molded will carry on the ideals, the power and the spirit which are so essentially yours. But the greatest contribution you have made to us all is the example of your blessed serenity in the midst of a tremendously full life.

# MUSCLE TRANSPLANTATION FOR COMBINED FLEXION-INTERNAL ROTATION DEFORMITY OF THE THIGH IN SPASTIC PARALYSIS

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Cases of cerebral spastic birth palsy not infrequently present the problem of the management of a flexion-internal rotation deformity of the thigh. In spite of prolonged training of muscles, it may be necessary to resort to operative procedures to improve muscle balance and relieve the deformity. In this paper I shall describe an operation used by me for the past ten years for the relief of this type of deformity. In this operation the muscles causing the deformity are transposed from their site of origin and attached to a new site on the ilium. In the new position they act as abductors, external rotators and extensors of the thigh.

## MUSCLES INVOLVED IN SPASTIC DEFORMITY OF THE THIGH

The cerebral lesion of spastic birth palsy is usually sufficiently diffuse to impair the function of groups of muscles. A single deformity is not as common as is a compound one in which several or all of the muscles about the hip are involved. The deformity of flexion-adduction-internal rotation is common. The predominant element may be adduction, it may be flexion, or it may be internal rotation.

If the predominant spasticity is that of the adductor group of muscles, satisfactory relief may be secured by adductor tenotomy and obturator neurectomy. This spastic deformity of the thigh is indeed the most common and this operative procedure the most satisfactory for its relief. It should be remembered, when adductor tenotomy is proposed, that the adductor magnus muscle is one of the prime extensors of the hip.<sup>1</sup> Therefore, if its tendon is severed, the power of active extension of the hip may be seriously impaired.

Internal rotation unaccompanied by other motion of the hip is produced by contraction of the anterior portions of the gluteus medius and minimus muscles. In the combined movements of internal rotation and hip flexion the tensor fasciae latae muscle also is called into action. Clinical observation of cases of cerebral spastic birth palsy in which there is the combined deformity of flexion and internal rotation leads to the conclusion that spasm of the tensor fasciae latae muscle is often a dominant factor.

Of the various operations for the relief of internal rotation deformity, the one devised by Durham<sup>2</sup> seems to yield the best results of any yet described. It consists of tenotomy of a portion of the gluteus medius and minimus muscles at their insertion into the great trochanter and division of the fascia lata at the same level.

Following the general observation that the antagonists of spastic muscles are weaker than normal, the extensors, abductors and external rotators of the thigh are usually impaired in power when there is spastic flexion-adduction-internal rotation contracture. One of the dangers in tenotomy of the gluteus medius and minimus tendons for the relief of internal rotation deformity (as pointed out by Durham) is that abductor power may be weakened. The operation described in this paper has the effect of reinforcing the power of abduction, external rotation and extension and at the same time diminishing the power of flexion and internal rotation. There-

1. Wright, W.: *Muscle Function*, New York, Paul B. Hoeber, 1928.

2. Durham, H. A.: A Procedure for the Correction of Internal Rotation of the Thigh in Spastic Paralysis, *J. Bone & Joint Surg.* 20:339 (April) 1938.

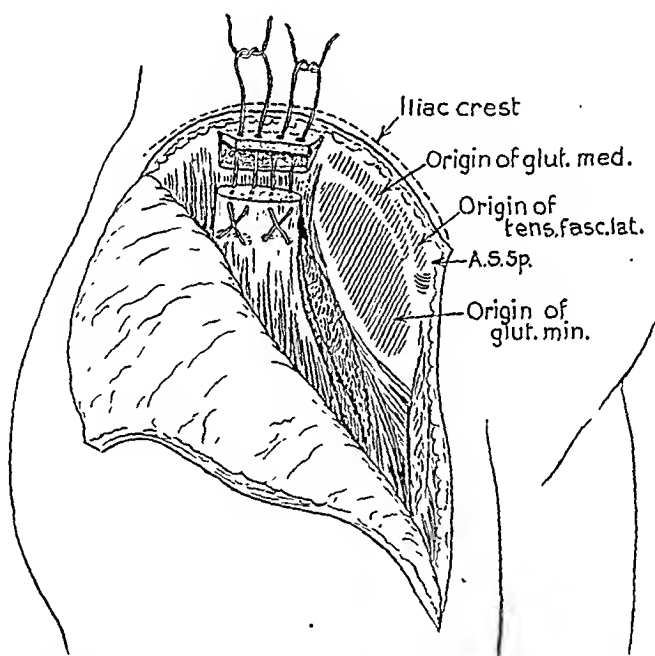
fore, on theoretic grounds it would appear to be superior to simple tenotomy of the overactive muscles.

#### SELECTION OF CASES

If the patient's chief motor disability is athetosis, or if he is suffering from a progressive degenerative lesion of the central nervous system, the operation is contraindicated. Suitable cases are those in which there is true spastic cerebral birth palsy or a static acquired lesion of similar character. The chief elements in the deformity should be flexion and internal rotation of the hip. Severe adduction deformity should be corrected by tenotomy and obturator neurectomy. This may be done at the same time as the transplantation or preliminary to it. The operation should be reserved for patients with reasonably good mentality who have the ability to walk.

#### OPERATIVE TECHNIC

The operation is similar to and was inspired by that originally described by Legg<sup>3</sup> for weakness of the abductor muscles of the thigh in infantile paralysis, but



Operative sketch showing the approximate amount of muscle transposed and the method of securing the free end of the muscle to the ilium.

differs from it in several essential features. It consists in freeing the tensor fasciae latae, together with the anterior third of the gluteus medius and minimus muscles, from their iliac origins and reattaching them to the ilium at a point slightly posterior to the great trochanter (fig.).

1. With the patient under general or spinal anesthesia and lying on the side opposite that of operation or in a hip trough,<sup>4</sup> a generous field is prepared. This should extend from the lower ribs to the knee, including the whole thigh, and from the midline of the abdomen anteriorly to the midline of the back. The leg is draped separately, so that it can be manipulated during the operation. Severe adductor spasm must be overcome by adductor tenotomy and/or obturator neurectomy before proceeding with the operation.

3. Legg, A. T.: Tensor Fascia Femoris Transplantation in Cases of Weakened Gluteus Medius, *New England J. Med.* 209:61 (July 13) 1933.

4. Gill, A. B.: Personal communication to the author.

2. The operative incision begins at the posterior superior spine of the ilium and curves forward along the iliac crest to the anterior superior spine. From that point it is extended downward and slightly outward on the anterior part of the thigh for about 6 to 8 inches (15 to 20 Cm.). After the incision is carried down to the deep fascia, the cutaneous flap is reflected from the underlying tensor fasciae latae muscle.

3. The anterior edge of the tensor fasciae latae muscle is freed distally to the point at which the ascending branch of the anterior femoral circumflex artery comes into view. Beginning inferiorly at the anterior edge of the muscle, the operator frees its under surface, carrying the dissection from below upward. Freeing the posterior margin of the muscle is unnecessary, and, if attempted, there is danger of damaging its nerve and blood supply. As the dissection is carried above the great trochanter, the anterior border of the gluteus minimus muscle is defined. A muscle mass consisting of the whole of the tensor fasciae latae muscle and the anterior third of the gluteus minimus and gluteus medius muscles is freed from its iliac origin (fig.). Two or three traction sutures are secured to the free end of the muscle mass.

4. The new site for attachment of the muscle is selected in the following manner: As an assistant holds the leg with the knee extended and the thigh in 20 degree abduction and full extension but neutral as regards rotation, the operator transposes the muscle mass so that it lies in greater part posterior to the coronal plane of the trochanter and pulls its free end as near the iliac crest as its length permits. This point is the site selected for the new origin of the muscle. Usually the muscle is too short to reach the iliac crest, but occasionally it can be attached there. The bed for insertion of the muscle is prepared as shown in the sketch (fig.). A slot  $\frac{1}{4}$  inch wide and  $1\frac{1}{2}$  to 2 inches long (0.6 cm. wide and 4 to 5 cm. long) is cut in the outer table of the ilium. The superior margin of the slot is levered gently outward after the making of divergent cuts  $\frac{1}{2}$  inch long at the two ends of the slot.

5. The free ends of the silk traction sutures are passed by a curved needle into the slot to emerge from drill holes in the outer table of the ilium. The free end of the muscle mass is then carefully drawn into the slot and the sutures are tied as the leg is held in the corrected position.

6. The wound is closed in layers and the leg is immobilized in plaster in the abducted, fully extended and slightly externally rotated position.

#### AFTER-CARE

Assisted motion and gentle physical therapy may be instituted as soon as the wound is well healed. Full weight bearing is permitted four to six weeks after operation. The extended, abducted and externally rotated thigh may be maintained in this position at night for as long as the surgeon deems advisable, but prolonged use of retentive apparatus is usually unnecessary.

#### RESULTS

Each of the patients operated on by me over the past ten years has obtained a satisfactory result so far as correction of the flexion-internal rotation deformity is concerned. Two additional patients whose cases have already been reported in the literature<sup>5</sup> have also had satisfactory results. The effect of the operation is most easily estimated by comparing preoperative and postoperative motion pictures of the patient in the act of walking. Owing to the fact that I am in military service, my records are not now available, and the exact date of the first operation, the number of patients operated on and other data cannot be ascertained at the present time. The operation rests on sound theoretic considerations; it is not difficult and in my hands it has yielded results superior to those obtained from other methods.

(The opinions and assertions contained in this article are the private ones of the writer and are not to be construed as official or as reflecting the views of the Department of the Navy.)

5. Green, W. T., and McDermott, L. J.: Operative Treatment of Cerebral Palsy of Spastic Type, *J. A. M. A.* 118:434 (Feb. 7) 1942.



## NOTES ON AN EARLY BONE CYST

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Solitary bone cysts are common, but serial roentgenograms showing their early rate of growth are not numerous, and seem worthy of publication.

The Institute of Child Welfare of the University of California, in Berkeley, has been closely following the development of certain pupils in schools, and among

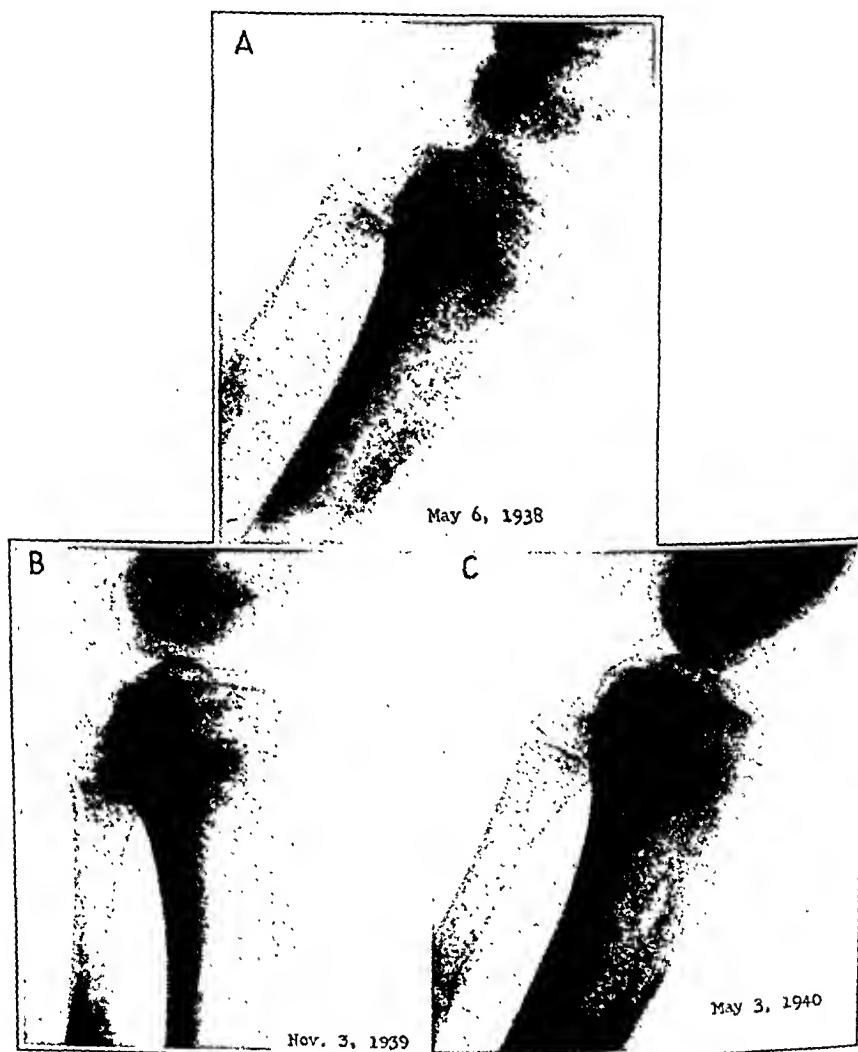


Fig. 1.—*A*, roentgenogram of the tibia that later was to show a bone cyst; the bone appears entirely normal. *B*, roentgenogram taken eighteen months later, showing a tiny bony defect near the medial surface of the tibia. *C*, roentgenogram taken a half year later than *B*, showing a bone cyst in the same location.

the methods used is the taking of serial roentgenograms of the left knee. In the course of the routine studies the cyst to be reported was discovered, and the Institute permitted me to use its data.

## REPORT OF A CASE

D. C., the boy in question, was a healthy active lad who had successfully weathered the usual childhood diseases. He had had no major accidents and no injury of any kind to the region of the left knee. The first roentgenograms were taken on May 6, 1938, when the boy was 9½ years of age. Both the anteroposterior and lateral views included the desired area of the tibia and showed the bone to be entirely normal (fig. 1*A*). The second roentgenograms were taken on Nov. 3, 1939, when the boy was 11. The anteroposterior view did not satisfactorily include all the desired area, but the lateral view did (fig. 1*B*). A tiny bony defect was seen. The next roentgenograms were taken a half year later, on May 3, 1940. In these

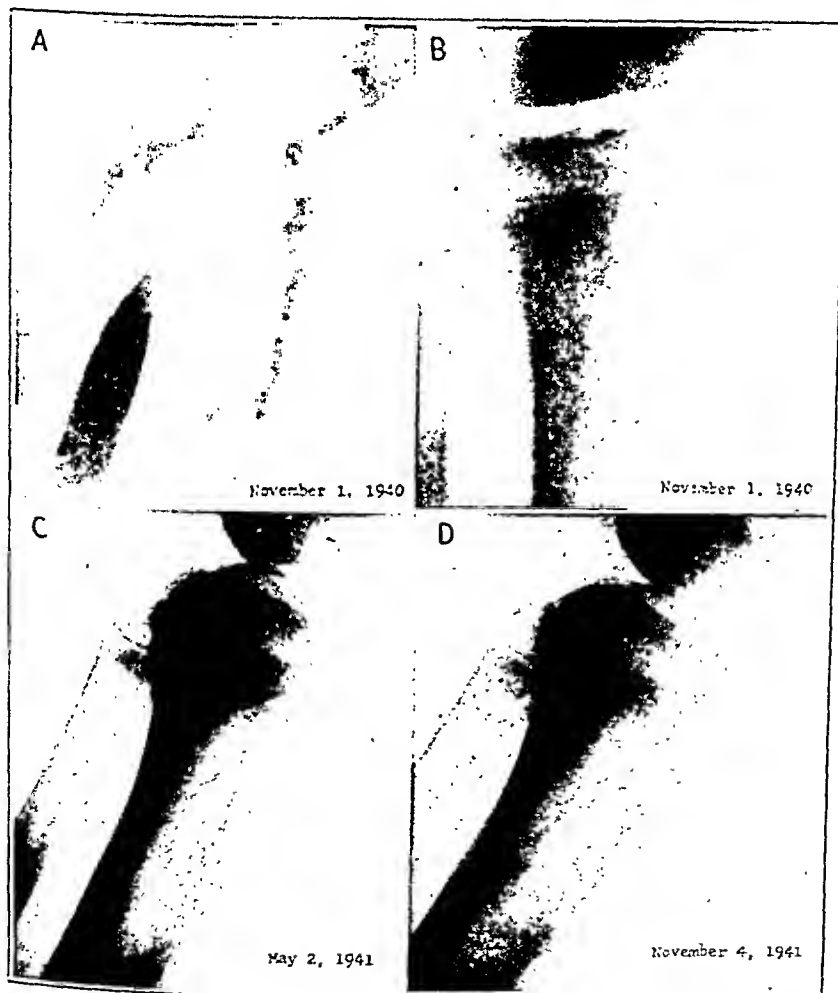


Fig. 2.—*A*, *B* and *C*, roentgenograms taken six months (*A* and *B*) and one year (*C*) after that shown in figure 1*C*. Three months later the cyst was treated surgically. *D*, taken two and a half months after operation, shows appearance of satisfactory healing.

a small area of rarefaction about 13 by 3 by 3 mm. in size (beginning of a cyst) could be seen near the medial surface of the tibia, commencing about 3 cm. distal to the proximal epiphysal line (fig. 1*C*). The anteroposterior view included only a portion of this cyst. Other roentgenograms taken on Nov. 1, 1940 and on May 2, 1941 showed considerable increase in the size of the cyst (fig. 2*A*, *B* and *C*).

On Aug. 15, 1941 the cyst was opened, curetted, swabbed with 50 per cent zinc chloride solution, washed with alcohol and closed. The wound healed promptly. The last roentgenograms taken about two and one-half months later, on November 4, showed satisfactory healing (fig. 2*D*).

The scrapings obtained at operation were immediately sent to the Alta Bates Hospital Laboratory, which made the following report:

"Macroscopic examination: The specimen consists of many small masses of hard and soft red tissue, weighing about 5 Gm. in all. Sections are taken for microscopic study.

"Microscopic examination: There is marked absorption of bone, and the soft tissue is of two distinct types. Some of the soft tissue is composed of a rather dense, regular, hyaline connective tissue, while the rest is composed of very cellular tissue containing many giant cells. The other cells are oval or spindle shaped with pale nuclei like endothelial nuclei. They are not malignant in appearance. The tissue is very vascular, and a considerable amount of brown blood pigment is present.

"Diagnosis: Giant cell tumor of bone. "Signed: David Singman, M.D., Pathologist."

#### COMMENT

This cyst was located in one of the three commonest sites for such lesions, which, according to Geschickter and Copeland,<sup>1</sup> are, first, the proximal portion of the femur, second, the proximal portion of the humerus and, third, the proximal portion of the tibia. The authors cited have described the acute bone cyst of not more than six months' duration as bordering "directly on the epiphyseal line on its shaft side." The present cyst was located obviously in the same general position, but even when first discovered it did not seem to border directly on any epiphysal line.

The data on hand are manifestly insufficient to permit exact determinations of the rate of growth in volume of the cyst, but since the roentgenograms were made under similar routine conditions, one could (by measuring in millimeters the three dimensions of the cyst as shown in each of the three sets of roentgenograms taken in May 1940, November 1940 and May 1941) get figures which would indicate not the actual volumes but approximately the relative sizes of the cyst on the two latter dates for comparison with that on the first date. The product of the three dimensions for May 1940 was about 126, that for November 1940 was about 500 and that for May 1941 was about 1,540. This seems to indicate that the volume of the cyst increased about 300 per cent during each of these two six month periods.

At no time previous to the operation did the boy have the slightest pain, discomfort or abnormal feeling of any kind about the lesion, nor was there any deformity, swelling or other local sign. The discovery of the cyst was entirely due to the fortunate routine roentgen examinations.

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1. Geschickter, C. F., and Copeland, M. M.: Tumors of the Bone, New York, American Journal of Cancer, 1931.

## DYSMENORRHEA: THE RESULT OF A POSTURAL DEFECT

LIEUTENANT H. E. BILLIG JR. (MC), U.S.N.

"Menstrual cramps and backache" have persistently played a prominent role among the chronic complaints that periodically interfere with feminine activities. Numerous investigations, in a search for causes and cures, have left a variety of theories which have obscured the factors involved.<sup>1</sup> By the use of fundamental methods of physical diagnosis, accurately applied, certain pertinent factors not heretofore generally recognized have been brought to light concerning dysmenorrhea.

In the examination at the time the complaints are present it can be noted that:

1. The localization of the pain of "abdominal cramps" is along the twelfth dorsal or the first lumbar spinal nerves or both, or along their branches, the ilioinguinal and iliohypogastric nerves, or along all these. Hence the symptoms are localized in relation to the peripheral nerves in the abdominal wall and not in relation to intrapelvic structures.<sup>2</sup>

2. The localization of the pain in the back is in relation to the region of attachment of ligamentous skeletal structures, e. g., ligamenta flava.

3. There is a restriction of the range of excursion in the posterior tilt of the pelvis in relation to the legs and the spine. If the posterior tilt of the pelvis is forced past the point of restriction by manipulation, the pain in the back and in the lower abdominal region is exacerbated. The manipulative testing is done by forced adduction in hyperextension of the leg on the pelvis with the patient lying face down on the table and the pelvis fixed firmly to the table by means of a strap placed at the level of the tip of the sacrum. The complaints can be elicited by this manipulative testing in any other phase of the estrus cycle even though the woman has never had them at other than a specific time in relation to the menstrual flow. The restriction of motion can be determined by this manipulative testing to be ligamentous and not bony. Careful test use of estrogenic substances reveals that the restriction of the posterior pelvic tilt is reduced when the estrogenic level is raised. This perhaps explains why the signs and complaints are most frequently present near the onset of menstrual flow, a time in the estrus cycle when the estrogenic level is lowered.<sup>3</sup>

A review of the illness in question in large series of cases of dysmenorrhea reveals that in addition to the "menstrual cramps and backache" there are a number of concomitant complaints frequently recorded. These include:

1. Aching and pain along the course of branches of the sciatic nerve, chiefly in the posterior tibial region.

2. Aching and pain in the occipital region of the skull (usually termed "headache") and the posterolateral region of the neck, sometimes radiating out to

1. Fremont-Smith, M.: Essential Dysmenorrhea, *New England J. Med.* 226:795-798 (May 14) 1942.

2. Billig, H. E., Jr.: Back Pain and Neuritis, *Am. J. Clin. Med.* 48:96-99 (April) 1941.

3. Hisaw, F. L.: Corpus Luteum Hormone: Experimental Relaxation of Pelvic Ligaments of Guinea-Pig, *Physiol. Zool.* 2:59-79 (Jan.) 1929.

the shoulders and arms. These complaints can also be exacerbated in testing by placing a manipulative tension on the ligamentous structures, past and through which the nerves supplying these regions course.

A postural defect of contracted ligamentous bands restricting the normal range of spinal-pelvic-femoral postural excursion is found present. The shortening or contracture of the ligaments causes compression of nerve pathways producing irritation of peripheral nerves. This irritation gives rise to painful symptoms in the region of the distribution of these nerves and is proposed as the mechanics involved in producing symptoms of dysmenorrhea.

Factors predisposing to the development of the postural defect include slumped posture in childhood; poor adult postural habit; occupational postural habit; slumping due to debilitation after illness; structural bony defects; paresis or paralysis; visceral irritations, such as endometriosis or pelvic inflammatory disease; endocrine shortcomings; fascial contracture subsequent to traumatic fascial strain; arthritis; lesions of bones and joints.

Treatment consists in freeing the nerves of their irritative compression by correcting the postural defect. This is done through precise routine ligamentous stretching exercises carried out by the patient, which result in progressive, accumulative lengthening of the ligaments involved.

The patient stands with heels and toes together about 18 inches (45 cm.) from, and with side to, a wall. The elbow is placed against the wall at shoulder level with the forearm and hand resting on the wall. The heel of the opposite hand is placed in the hollow on the posterior aspect of the greater trochanter of the hip. The shoulders are kept in a line with the elbow perpendicular to the wall and not allowed to shift forward. The knees are kept completely extended and not allowed to flex. The abdominal and gluteal muscles are strongly contracted while the hips are shifted slightly forward and in toward the wall, aided by pressure on the greater trochanter of the femur from the heel of the hand. The objective is to force the extent of sideward and forward shift of the hips in toward the wall far enough not only to place a strain on the contracted ligamentous bands but to gain a progressive stretch as well. This accentuates the symptoms momentarily at each stretch. The stretchings are done routinely three times to each side at three periods daily, a total of nine stretchings to each side every twenty-four hours. When these stretchings are being taught, the patient must return for instruction at two day intervals several times, with weekly observations thereafter, else the stretchings will frequently be done incorrectly or incompletely and the expected benefits will not be obtained.

With consistent stretching, complete lasting relief will usually be obtained (1) in mild cases after about one month, (2) in moderately severe cases after about two months and (3) in severe cases after about three months. An occasional patient will need the additional aid of estrogenic therapy. After relief has been obtained the patient is advised to continue the stretching exercise sufficiently to "keep stretched out," in order to prevent recurrence.

The method has been applied and evaluated in several health services and by several observers as follows:

For nearly three years the stretchings have been used routinely in the Woman's Student Health Service at the University of Southern California, in Los Angeles, under the supervision of Prof. Lucile Gruenwald, assistant supervisor of physical education for women. Professor Gruenwald reports:

... every girl who has conscientiously done these stretchings has obtained complete relief. We are very enthusiastic and are making knowledge of this method available to our classes for physical education teachers.

Mr. John C. Burke, assistant director of the health service section of the Los Angeles City School System, reports on the use of this method as follows:

During the last three months of the past school year, ten senior high and three junior high schools incorporated your special exercise program in their corrective procedures. There were 625 girls enrolled, chiefly the severely affected. Of these 80 per cent were reported cured or improved. The other 20 per cent were those who did not follow the program scheduled or who were indifferent. Our teachers are very enthusiastic about the exercises and are encouraged because of the outstanding results obtained. We are including them in the corrective physical education program of all our junior and senior high schools.

For the past two years the method has been in effect at the Parent-Teacher Association Health Center for the Los Angeles City Schools under the guidance of Supt. R. P. Deakers, M.D., and the chief supervising nurse, Mrs. Ethel L. Huston, P.H.N. They report that cooperation of girls under treatment has been good and that relief of the complaint has been effected in all those who cooperated.

The Twentieth-Century Fox Studios have, for the past year, used the method under the supervision of Mrs. Kathleen Ridgeway, who reports routine alleviation of the complaint in her cases and states that the loss of innumerable work days due to this complaint have thus been eliminated.

Defense industries, faced with the problem of keeping an increased percentage of women workers on the job, have installed the method in order to eliminate periodic off-duty days. Dr. A. C. Dick, medical director of Consolidated Aircraft Corporation, of San Diego, Calif., arranged for instruction of the plant nurses and matrons in the use of the method. Dr. Dick reports that in every instance in which the woman has done the stretchings consecutively for forty-five days there has been marked relief.

#### SUMMARY

The postural defect of contracted ligaments giving rise to irritative compression of nerves is proposed as the cause of the symptoms of dysmenorrhea.

A practical method of releasing the irritative compression of nerves by loosening the ligaments involved through accumulative routine stretching is outlined.

#### COMMENT

Although a clinical method of relief from dysmenorrhea is at hand, the subject awaits adequate explanation of the physiologic mechanism of the localized radiation of pain along the course of a peripheral nerve. The exact physiologic-anatomic mechanism of shortening and lengthening of ligaments (e. g., ligamenta flava or the iliotibial band) needs explanation.

## EARLY MOBILIZATION OF FRACTURES OF THE UPPER END OF THE HUMERUS

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The following is a brief report of 97 cases of fracture of the upper end of the humerus taken from the orthopedic services of the Charity Hospital at New Orleans. The plan of treatment followed that of M. K. Lindsay and Carolyn M. Brown:<sup>1</sup> P. D. Wilson<sup>2</sup> and A. C. Schmidt.<sup>3</sup>

The fractures were located as follows: surgical neck, 61; greater tuberosity, 17; anatomic neck, 11; lesser tuberosity, 2; shaft, 6. (In approximately 50 per cent of all cases the fractured bone was comminuted.)

The methods of reduction required in some of the cases will not be discussed, but the fixation and the subsequent treatment to regain motion were carried out in accordance with the following methods:

The fractured extremity is supported by an axillary pad, with the arm fixed to the side of the body by a wide bandage encircling the upper arm and the body, leaving the elbow free. The wrist is supported by a cuff suspended from the neck. When in bed, the patient is placed with the body at approximately an angle of 35 degrees. It is important that the patient at no time be placed in the horizontal position. The physical therapy as carried out by the physical therapy department at Charity Hospital is as follows:

The day after the fracture mild, dry heat is applied to the shoulder, elbow and hand without disturbing the bandage. On the fourth day after the application of heat the bandage is removed with the patient in a standing position. Light effleurage of the entire extremity and shoulder is administered to relieve pain and reduce swelling, and at the same time the forearm is gradually extended. Following the massage, the patient is instructed to flex the trunk, bend the knee on the affected side and permit the affected arm to fall forward completely relaxed, so that passive abduction and forward flexion are secured. The patient now moves the body in a circular motion so that passive circumduction of the shoulder occurs. The range of motion at first is small and is gradually increased. After five to seven days active motion gradually replaces passive motion. Strict supervision of this treatment is essential and should be carried out by a competent physical therapy technician. At the end of the treatment the axillary pad and the body bandage are replaced. Three or four weeks later the abduction pad and the bandage are discarded, and the forearm cuff, a week to ten days later. At the end of four weeks all active motion of the shoulder is encouraged. Treatment is continued daily for two weeks, then three times a week for two weeks, twice a week for three weeks and once a week until satisfactory range of motion has been obtained. The average number of treatments required in the series of cases reported was twenty-three.

1. Lindsay, M. K., and Brown, C. M.: *Relaxed Motion in the Early Mobilization of Fractures and Dislocations*, in Mock, H. E.; Pemberton, R., and Coulter, J. S.: *Principles and Practice of Physical Therapy*, Hagerstown, Md., W. F. Prior Co., Inc., 1932, vol. 3, chap. 16.

2. Wilson, P. D.: *Experience in the Management of Fractures and Dislocations*, Philadelphia, J. E. Lippincott Company, 1938.

3. Schmidt, A. C.: *Physiotherapy Rev.* 19:65 (March-April) 1939.

The range of motion is graded as follows: 0 to 25 equals poor; 25 to 50 equals fair; 50 to 75 equals good; 75 to 100 equals excellent.

The results obtained have been as follows: Poor in 6 cases, fair in 17, good in 32, excellent in 27 and undetermined in 15.

Lack of cooperation and failure to report back for treatment accounted for a large majority of the "poor" and "undetermined" results.

This method in my opinion is far superior to the old method of long immobilization because no elaborate equipment is necessary, patients do not need to remain in bed, they are comfortable almost from the start of treatment, pain is promptly relieved and later complications, such as stiff joints and traumatic arthritic changes are seldom seen.

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# PRONE POSITION FOR EXPOSING THE MEDIAL MENISCUS OF THE KNEE JOINT

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Numerous types of incision have been described in the past for removal of the menisci of the knee joint. There is first the utility or paramedian incision which skirts the mesial border of the patella and divides the tendon of the quadriceps muscle. This incision, while it is used often, has the objection of causing a long disfiguring scar.

Proper names are deservedly disliked in medical literature, but the following names have been popularly attached to types of incision for removal of the internal semilunar cartilage of the knee joint. The curved incision described by Jones (fig. 1, 1) is possibly the most popular for excision of the medial meniscus of the knee joint. The Jones<sup>1</sup> incision is "slightly curved and extends from an inch within the lower angle of the patella to one-half inch below the tibial margin, curving more acutely at this point toward the internal lateral ligament."

The Cave<sup>2</sup> incision was described as follows: "The incision begins three-eighths of an inch behind and on a level with the internal epicondyle of the femur. This incision is carried downward and curved gradually anteriorly to a point one-fourth inch below the joint line and then forward to the border of the patellar tendon" (fig. 1, 2).

Fisher<sup>3</sup> described his incision as follows: "This is a curved incision. The more vertical element of the curved incision coincides with the anterior margin of the internal lateral ligament and the horizontal element curves forward toward the patellar ligament" (fig. 1, 3).

Bristow<sup>4</sup> uses a simple oblique incision on the anteromesial aspect of the knee joint. His incision is practically transverse.

I do not intend to confuse or complicate the simple task of excising a meniscus of the knee joint by proposing a new incision. In the method to be described, the principal feature is the patient's position on the operating table. The patient is placed in a prone position on the operating table (fig. 1, 4). The knees are kept flexed on the thighs. First the sound knee is kept flexed by a bandage tied from the ankle to the head of the operating table. Next the operative site is prepared while an assistant holds the leg aloft. Draping of the knee is finished, and the draped knee is kept flexed by tying a sterile bandage from the ankle to the head of the operating table. No tourniquet is used for fear of the development of thrombosis of the popliteal artery. Murray<sup>5</sup> pointed out that bleeding into the knee joint from an incision will be negligible if the patient is operated on in the Trendelenburg position.

1. Jones, R., and Lovett, R. W.: *Orthopedic Surgery*, New York, William Wood & Company, 1923, p. 34.

2. Cave, E. F.: Combined Anterior-Posterior Approach to the Knee Joint, *J. Bone & Joint Surg.* **17**:427-430, 1935.

3. Fisher, A. G. T.: *Internal Derangements of the Knee Joint*, New York, The Macmillan Company, 1924, p. 61.

4. Bristow, W. R.: *Internal Derangements of the Knee Joint*, *J. Bone & Joint Surg.* **17**:605-626, 1935.

5. Murray, C. R.: Complicating Factors in Treatment of Injuries to Menisci of Knee Joint *Am. J. Surg.* **55**:262-273, 1942.

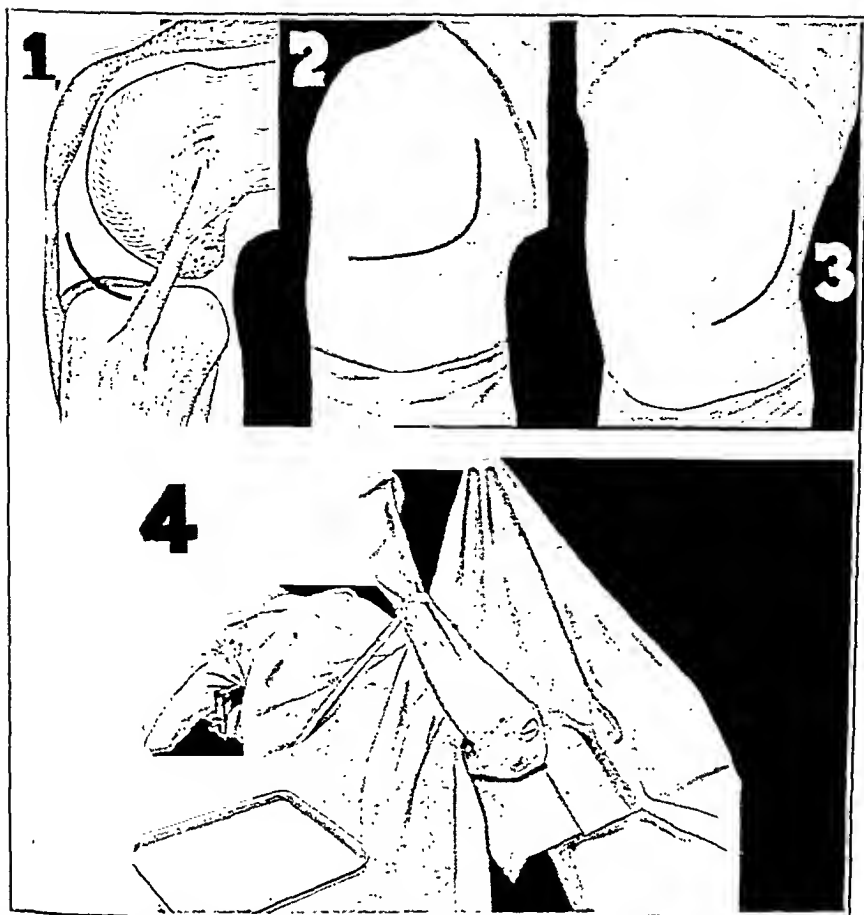


Fig. 1.—(1) Jones incision for removal of the medial meniscus of the knee joint; (2) Cave incision; (3) Fisher incision; (4) prone position and transverse incision described in this article.



Fig. 2.—Visualization of the medial meniscus at operation.

With the patient prone and with his knees flexed, the operator makes his incision. I prefer a small transverse incision directly over the proximal end of the tibia. This incision extends along the anteromesial edge of the tibia for a distance of about  $1\frac{1}{2}$  inches (3.8 cm.). After the incision is deepened through the superficial and deep fascia, the synovial membrane is incised exactly at the articular surface of the tibia. The torn meniscus can now be visualized and excised. Should insufficient exposure follow the use of the incision, a second incision may be made anterolaterally over the lateral semilunar cartilage. In addition the knee joint may be extended in order to expose the popliteal area for incision. Neither of these incisions has been necessary in the present series.

I believe that by operating with the patient prone the posterior portion of the meniscus can be seen more easily than by an incision of similar size with the patient in a supine position. In the prone position the knee joint can be completely flexed. The tibia can be used as a lever by the assistant to abduct the knee joint; thus the mesial compartment of the knee joint can be fully visualized.

In the description the preparation for surgical intervention may seem complicated and laborious, but this is not actually the case. The patient should be so placed that his knees project just beyond the end of the operating table. (The leaf of the operating table should be dropped before the patient's leg is prepared.) Shoulder bars will prevent the patient from sliding toward the head of the table. The foot of the operating table is raised considerably.

An objection that may be raised to operating on a patient in the prone position is the difficulty of administering an anesthetic. I encountered no difficulty when spinal anesthesia was used.

Fifteen patients have been operated on in the manner described. The methods of immobilizing their knees postoperatively have varied. No fixed conclusion has been reached as to the best method of immobilizing knee joints after arthrotomy.

#### SUMMARY

The prone position for excision of the medial meniscus of the knee joint has been described. Exposure of the posterior half of the meniscus is facilitated by this procedure.

# NEW ASPECTS OF SPINAL INJURIES

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This article has for its purpose the recording of (1) points concerning the treatment of spinal injuries on which general agreement has been reached, (2) points on which there still exists considerable divergence of opinion and (3) a number of new aspects which may be considered addenda to the general subject of spinal injuries.

The treatment of fractures and fracture-dislocations of the spinal column from remote antiquity to the present day divides itself naturally into four periods. Historical data revealed by the findings of Dr. George Bennett show throughout periods covering millenniums many an attempt at immediate reduction, some of which apparently were completely successful. All such attempts, however, were done blindly, and photographic proof obviously is completely lacking. Professor Roentgen's discovery in 1896 provided the only exact criterion for diagnosis and perfection of result. The orthopedic surgeon had been treating tuberculosis of the centrum for ages, and many had been the attempts to correct the hunchback. The failure of the centrum to repair its defects, however, led to a misapprehension regarding the callus-forming ability of the vertebral body, so that any attempt to open up a collapsed centrum was frowned on if not actually forbidden. Had it not been for this very naturally acquired misconception, the problem of the crush fracture of the centrum probably would have arrived at a much earlier solution. The ancients experienced no such conditioning, and by and large it might be said that they treated fractured spinal vertebrae more rationally than did, later, surgeons who operated during the intermediate modern period when the association complex of pathologic destruction of the substance misled them into funny ideas about the circulation of the centrum being peculiar. The idea that the centrum or body of the vertebra constituted the one outstanding exception to spontaneous callus formation became fixed.

The modern conception of Kümmell's disease served to intensify the illusion. Kümmell's disease was thought to be idiopathic or spontaneous progressive atrophy, its cause being vaguely related to injury. Subjected to the light of adequate roentgenography another boggy was dispelled. Kümmell's disease as such has now disappeared, the condition to which that name was applied having taken its proper position as an unrecognized or improperly treated fracture of the centrum. The subsequent atrophy is now interpreted as nothing more than nonunion due to motion between fragments with resulting failure of anastomosis of vessels between the two main fragments.

And then came fear. Fear of overhyperextension sufficient to disrupt the spinal canal, sufficient to induce paralysis. Tests of the tensile strength of the anterior longitudinal ligament, together with a study of its structure and of its behavior when fracturing forces were applied to the spinal column, demonstrated its relatively great strength. By and large one may say that the anterior longitudinal ligament is secure against horizontal severance as a result either of fracturing forces or of hyperextension reduction. With but two exceptions, the check strap function of the anterior longitudinal ligament can be depended on. The exceptions consist of the rare case

of hyperextension fracture and the case in which the horizontal element or shearing force has irreparably damaged the cord.

Seventeen years of experience in actual and immediate reductions of fractures and dislocations of the spinal column have served to bring about general agreement on a number of points. These points may be listed as follows:

1. Hyperextension is as generally applied in the reduction of fractures of the spinal column as is straight line traction in the reduction of fractures of long bones.
2. The vertebral centrum can be depended on to form callus after fracture as promptly as any other osseous structure.
3. In cases of paralysis laminectomy as a decompressive procedure occupies a place distinctly secondary to that of hyperextension.
4. The Queckenstedt test is an invaluable means for the determination of spinal subarachnoid block before and after hyperextension.
5. Skeletal traction, such as that obtained with the Crutchfield tongs, is an invaluable therapeutic adjunct for crush fractures or fracture-dislocations of the cervical part of the spinal column.
6. The intact posterior arches of vertebrae when hyperextended are capable of sustaining the imposed weight of the torso without the aid of the centrum; thus during part of the convalescent period the patient is made safely ambulatory.
7. The anterior longitudinal ligament when interpreted correctly acts as the main reducing medium as well as the main check strap opposed to excessive hyperextension.

At the present writing a number of points of disagreement may be mentioned. First among these points is that of convalescence. The questions of a rule of thumb regarding the amount of time spent recumbent and the amount of time ambulatory, the total time necessary for callus formation and the criteria by which one may judge the integrity and structural strength of callus have called forth widely divergent opinions. From the one extreme of allowing the patient to be ambulatory in a hyperextension jacket immediately after reduction to the other in which he is not allowed to be foot loose and free for six months or longer, many intermediate courses are practiced. Were it possible to exhibit adequate detail of the posterior arch roentgenographically, ambulatory treatment immediately after reduction would be understandable. Considerable evidence, however, exists to show that fissure fracture of the posterior arch occurs regularly, and with the presence of such a fracture, the possibility of a false joint with excessive callus in the articular processes and pedicle sufficient to encroach on nerve roots seems obvious. In my estimation weight bearing should be prohibited up to the time of differentiation of fibrous tissue into bone—in other words, approximately six weeks. On the other hand, results in some 250 cases of crush fracture of a vertebra demonstrate that if the rule of thumb of "six weeks recumbent and six weeks ambulatory in adequate hyperextension" is followed, the sequela of pain in the injured area does not occur nor is there subsequent wedging of the vertebra following the removal of the cast three months after fracture. The general rule therefore is that the patient after reduction of the fracture and application of an adequate hyperextension jacket is allowed freedom in bed to move about in the horizontal position as he pleases but is not allowed to sit up or stand up for six weeks and that then, provided his jacket fits properly, he is not only allowed but is encouraged to walk, as soon

as he can, up to two miles a day in order to induce structural trabeculation in the amorphous callus. It is found regularly and without exception that at the end of three months from the time of fracture an ordinary crush centrum of the vertebra has developed so sound a callus that no fear of a recurrence of collapse of the body need be entertained.

The other main point of disagreement is the manner in which reductions of compression fractures are done. A great variety of methods, all depending on hyperextension, are being used, the Watson-Jones method possibly as much as any. By using the standard hospital bed in reverse, the spinal column can be gradually hyperextended by simply turning the crank. Various types of jacks are

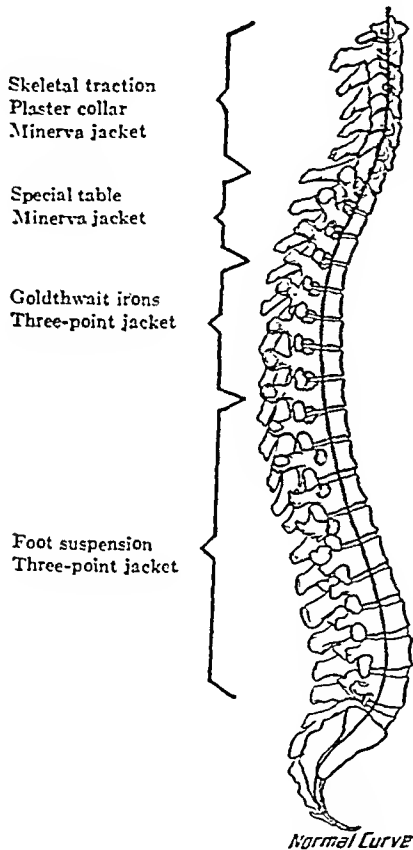


Fig. 1.—Difference in method indicated by difference in anatomy.

used by others. My experience in this connection is that the jack is very traumatizing, is extremely painful, requires the use of an opiate or an anesthetic and produces severe distention. Another method reduces the fracture by laying the patient supine, putting a band crosswise underneath the fractured area and hyperextending simply by elevating the band. Gradual methods obviously must be retained for cases of fracture-dislocation with paralysis in which hyperextension cannot be used or in which there are multiple other fractures and the spine meanwhile must be hyperextended. In these cases the standard adjustable hospital bed will suffice or a Rogers frame may be used. Rogers, Dunlop and Jones all have shown excellent results with their individual methods. After having tried all the methods mentioned, I have returned to foot suspension because of its being the simplest and

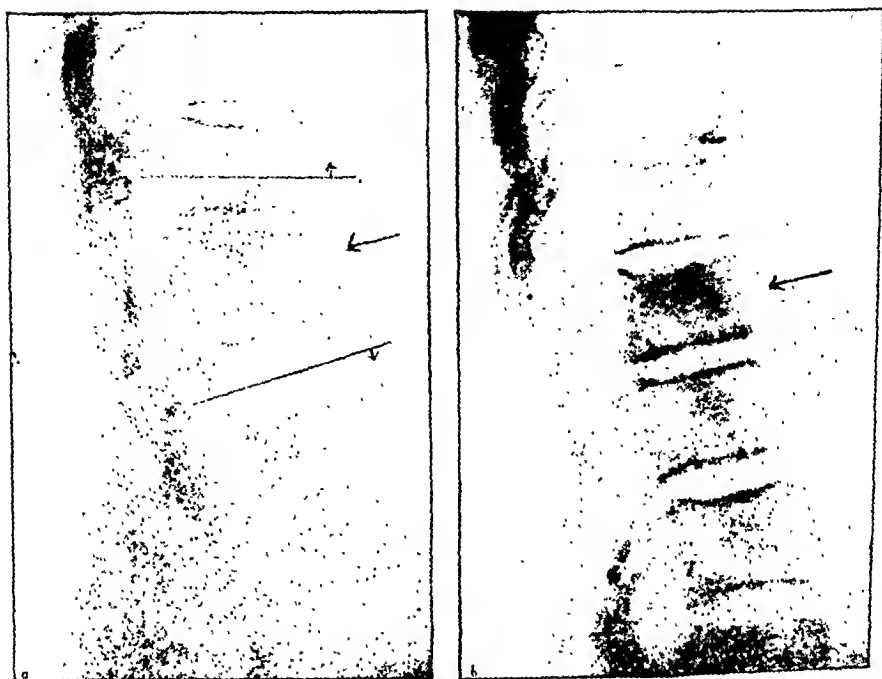


Fig. 2 (case E. G.).—(a) Typical crush fracture of the first lumbar vertebra. The levers illustrate the traction and the countertraction exerted by the vertebra above and that below the affected one. (b) Typical reduction by foot suspension.

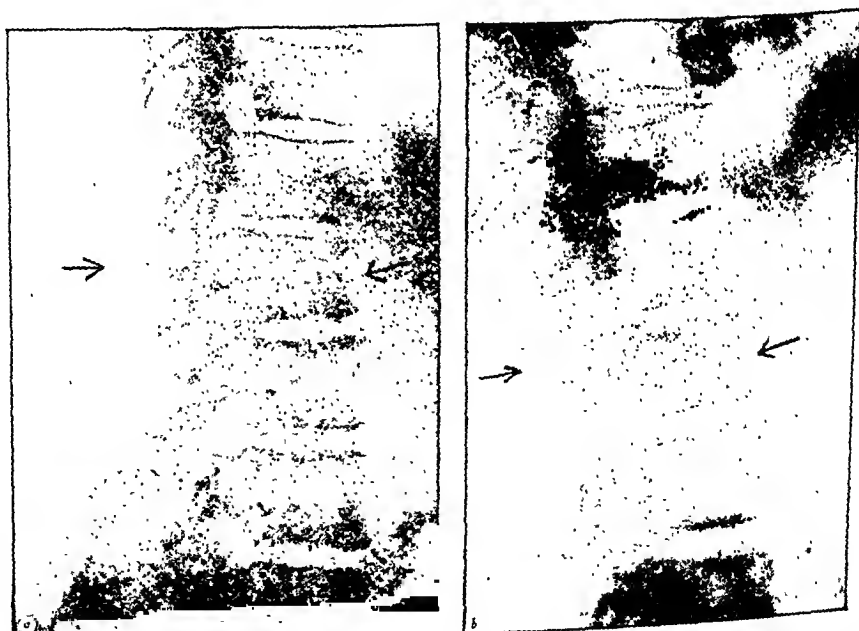


Fig. 3 (case A. H.).—(a) Very moderate uncomplicated compression of the first lumbar vertebra. (b) Result three months after reduction with Goldthwait irons. Note the complete restoration of the anterior vertical diameter.

the most effective as measured by ease of operation, degree of reduction and the critical factor of protection of the posterior arch. No opiate or anesthetic is used, and the patient's discomfort at the point of fracture is usually relieved during this simple gravity suspension.

In a personal communication from Dr. Gallie, of Toronto, Canada, I learned of a method which can be extemporized where the ordinary medical facilities are not available. If one recalls that hyperextension by foot suspension involves nothing more drastic than the child's game of wheelbarrow, fears concerning foot suspension should be dispelled. Dr. Gallie stated that treatment in his first case was carried out in the following manner: "A small box was placed under the chest of the patient, he lifted the feet to his shoulders and rested them there while an assistant put on a plaster jacket."

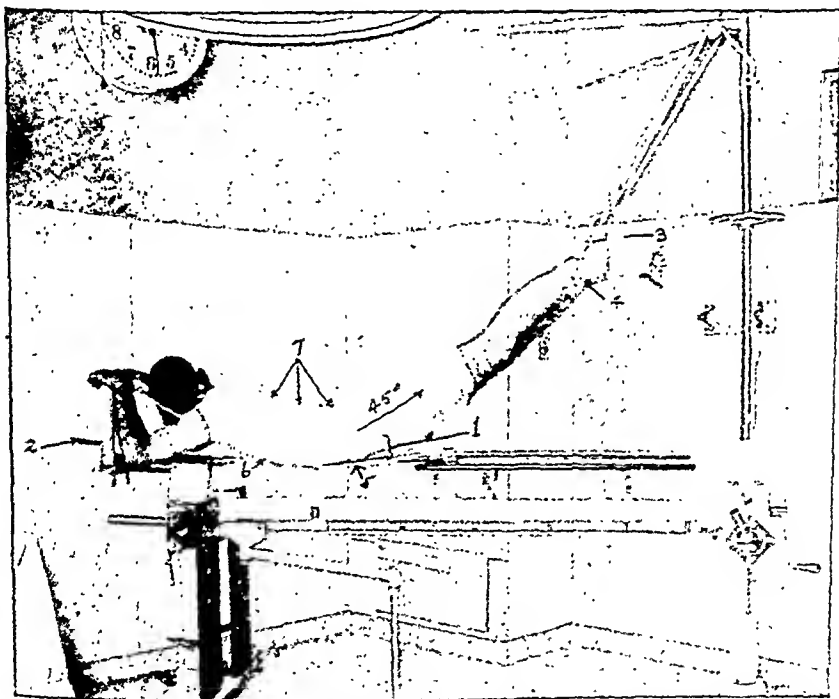


Fig. 4.—Points in a typical reduction of an uncomplicated thoracolumbar crush fracture: 1. Ample clearance between the anterior spines and the hammock affords an index of adequate hyperextension. 2. The hammock may be lowered with a crank to increase hyperextension further. 3. Sheet wadding cushions the holder. 4. A holder loop of canvas with a ring by which to suspend the patient is shown. 5. A canvas hammock is to be noted. 6. The weight of the chest is carried by the hammock. 7. Maximum hyperextension is obtained at the region involved.

#### SOME NEW ASPECTS OF SPINAL INJURIES

Several new accretions to the subject of spinal injuries have become apparent. These seem worth recording at this time.

1. Under the heading of roentgenographic concealment in relation to the *degree* of severity of the injury, new interpretations seem important.
2. The tests for the tensile strength of the anterior longitudinal ligament bear an important relation to the general subject and to the various technics employed to reduce fractures of the spinal column.



3. A method is presented for diagnosing by inference a fracture-dislocation in which there is a single jumped process.

4. A technic by which such a fracture-dislocation may be reduced completely is described.

5. The diagnosis and the treatment of a hitherto unrecognized but regularly occurring type of cervical luxation are presented.

By this time it has become obvious that the vast majority of crush fractures and fracture-dislocations of the spinal column occur as the result of a hyperflexion mechanism. The preponderance of the automobile accident as a cause of these fractures has helped to an understanding of the usual fracturing force. In a head-on collision the continuing forward momentum of the parts of the body that are not braced when the vehicle has come to a full stop results in a whip lash mechanism. The forward momentum of either the head alone or a part of the torso continues on the lower fixed section of the body at the moment of impact of the collision. Immediately following the hyperflexion there is a spontaneous recoil in extension. The complete action resembles a whip lash. The recoil mechanism is sufficient in some cases to reduce a dislocation spontaneously as evidenced by cases showing complete neurologic involvement from the cervical region downward, in spite of the first roentgenograms showing apparently negligible damage or no damage at all. Likewise, the spontaneous partial reduction of a crush fracture of the lumbar area is accomplished by proper first aid handling—e. g., by rolling the patient over and carrying him in the prone position—or simply as a result of his rising on his elbows in this position. Either or both of these actions exert enough extension to partly restore vertical diameter. It is clear, therefore, that the first lateral roentgenogram cannot be expected to show the full degree of involvement of the vertebral arch since it is not known how much spontaneous reduction already has taken place. The likelihood of involvement of the posterior arch is proportional to the degree of vertical collapse of the centrum. There is considerable evidence from those whose practice it was to expose such fractures for the purpose of immediate fusion that at the time of exposure a good many fissure fractures of the articular processes and laminae were disclosed which otherwise were unsuspected. The following section, therefore, is aimed at clarifying hidden lesions of this type.

#### ROENTGENOGRAPHIC CONCEALMENT

The diagnosing of lesions of the posterior arch by inference must be resorted to since the roentgenogram cannot be depended on to show even gross lesions involving the pedicles, the articular processes and the laminae. One is frequently tricked by the illusion of a completely normal-appearing posterior arch. Fissure fractures without gross displacement, for instance, are impossible to exhibit by ordinary roentgenography. Figure 5 depicts a portion of a spinal column (obtained at autopsy) in which a number of fractures of the pedicles and articular processes were made with a Gigli saw. The four views of this specimen show but two fractures. It is noted in this connection that the Gigli saw creates a considerably greater defect than a simple fissure fracture.

While it is generally appreciated that the roentgenogram cannot be expected to show all of the lines of fracture in a long bone, it is not so well known that cracks and dislocations of a posterior vertebral arch are much more effectively concealed than those of a long bone because of the very dense bone forming the

accessory processes and because of the number of such processes, particularly in the lateral plane. An Indian hiding behind the trunk of a tree or a barricade would photograph as readily.

A glance at the spinal column shows how impossible it is to hope to reveal the fracture or the dislocation by photography because of the number of processes to

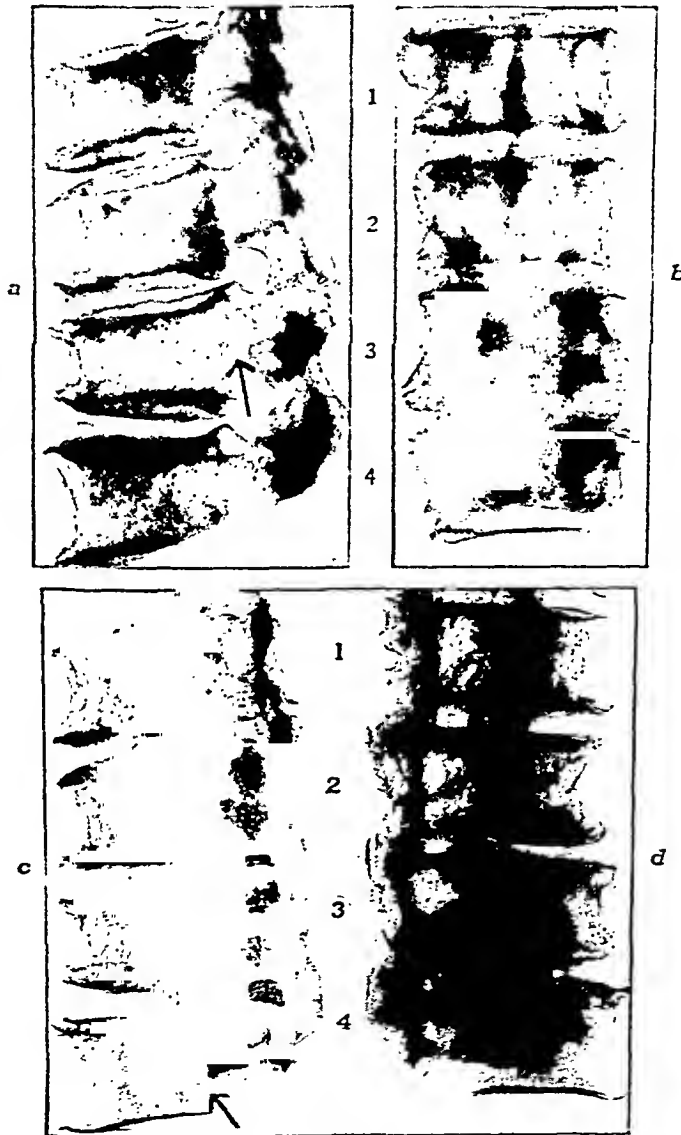


Fig. 5.—Roentgenographic concealment. The letters *a*, *b*, *c* and *d* indicate lateral, anteroposterior, left oblique and right oblique projections of the same portion of a spinal column obtained at autopsy. Fractures were made at various points in the posterior arch with a Gigli saw. A sample of the defect created by the saw is indicated by arrows. The other fractures contain the same amount of defect but are concealed by overlying dense bone. In *a*, *b*, *c* and *d* the states of the four vertebrae are as follows:

- | Left                                  | Right                          |
|---------------------------------------|--------------------------------|
| 1. Intact                             | 1. Articular process fractured |
| 2. Tip of articular process fractured | 2. Pedicle fractured           |
| 3. Intact                             | 3. Pedicle fractured           |
| 4. Articular process fractured        | 4. Articular process fractured |

be penetrated by the rays. In the lateral roentgenogram, for instance, it is necessary to penetrate both transverse processes and four articular processes, besides two pedicles. If a line of fracture shows, it is by the merest chance, and it is necessary for the defect to be large or the dislocation gross.

Roentgenograms taken at an angle of 30 to 40 degrees are more likely to exhibit fracture lines in the articular processes than lateral roentgenograms. The majority of such oblique views, however, cannot be expected to show much more than irregularity of the posterior articulations. The lack of visual evidence of fault in the posterior arch will continue to deceive most observers and will undoubtedly continue to create a false sense of security because of negative findings. No doubt greatly increased caution is exercised by most operators in their approach to frac-

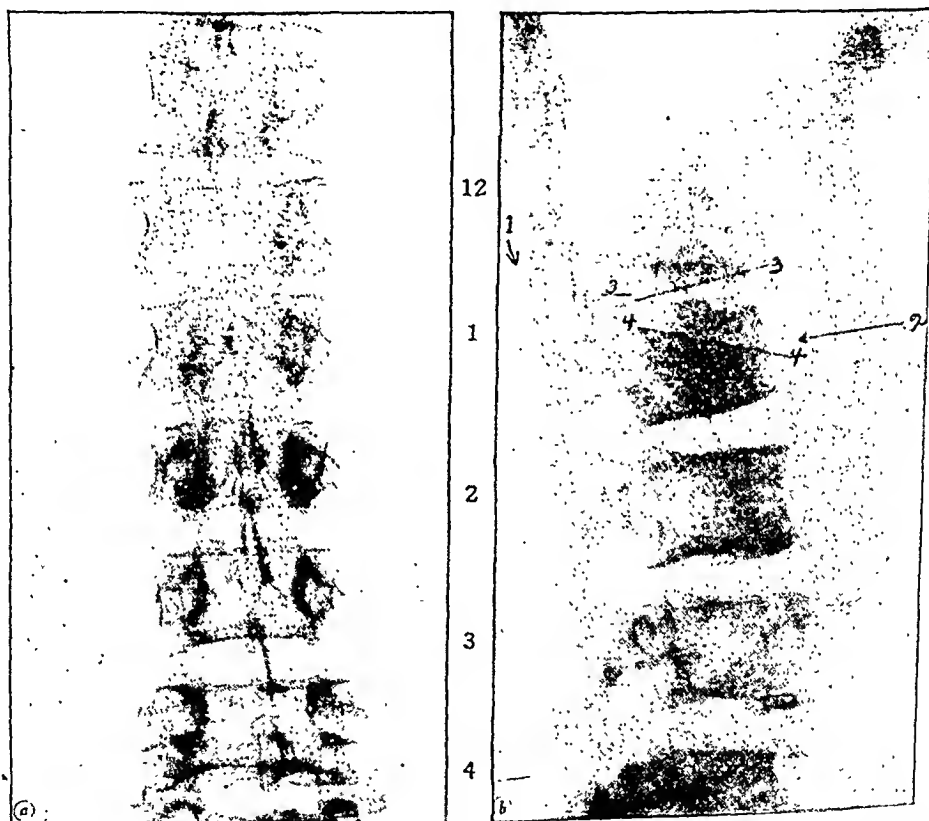


Fig. 6 (case B. G.).—(a) Anteroposterior projection of a spinal column showing fracture dislocation of the first lumbar vertebra. Note the lateral angulation, the wide space between the spinous processes, the different alignments of the series of spinous processes above and below the dislocation and the unequal compression of the two sides of the involved vertebral body. Compare with *b*. (b) Lateral projection: 1 indicates a gross enlargement of the intervertebral foramen. An articular process of the twelfth dorsal vertebra has dislocated upward and is impaled on the superior articular process of the first lumbar vertebra. 2 indicates the compression unreduced after an attempt at hyperextension. Impinging articular processes do not permit the normal fulcrum of the posterior joint to operate; therefore disimpaction is impossible until the processes have been disengaged. 3 indicates the level of one side of the crushed centrum. 4 indicates the lower level of the opposite side.

ture-dislocations with paralysis; it is the damaged cord in this case which warns the operator. Fracture-dislocations of fully as great magnitude but without paralysis occur regularly. In the case of paralysis one must assume risks which would not be warranted in the case of a simple crush fracture. The greatest danger,

however, is that the operator may do real damage to a fracture-dislocation *without* paralysis. Methods of identifying the dangerous types are as follows:

The roentgenograms must be scanned from the point of view of damage to the posterior arch. With this approach in mind, certain points become immediately obvious. The correlation of a number of these points will frequently decide whether the case is one for manipulative or one for operative procedure. By observing all roentgenograms of spinal injuries in this light, the operator will safeguard himself against disasters due to manipulation.

Figure 6 depicts a case of this kind clearly. The patient presented no neurologic signs whatever. Four points were noted in the anteroposterior view: (1)



Fig. 7.—Factors entering into the diagnosis of a fracture-dislocation of the lumbar region: (1) the lateral tilting of the twelfth vertebra; (2) the different alinelements of the upper and lower series of spinous processes; (3) the lateral angulation of the two spinal segments; (4) the rotation localized to the point of dislocation as indicated by the lateral offset of the twelfth vertebra and (5) the wide vertical separation of the twelfth and first spinous process.

lateral angulation with its apex at the twelfth interspace; (2) a wide interval between the spinous processes of the twelfth dorsal and the first lumbar vertebra; (3) definite rotation of the entire upper section as indicated by defective alignment of the upper series of spinous processes with those of the lower section; (4) unequal compression of the two halves of the body of the involved vertebra. The patient was a slender boy, i. e., the type of patient with whom roentgenography is at its best and shows the articular processes clearly.

The lateral view brings out additional points: at 1 gross enlargement of the intervertebral foramen; at 2 an appearance of one articular process being impaled

on the one below; at 3 and 4 an appearance of two different levels in the centrum. Wherever such a double shadow of a vertebra appears, dislocation of one articular process must be expected.

Figure 7 is an exact replica of the case just cited. When analyzed, this anatomic specimen shows the lower right process of the twelfth dorsal vertebra jumped and locked in front of the upper right process of the first lumbar vertebra. It also shows almost complete dislocation of the left process.

An analysis of this specimen shows why the angulation, the rotation and the disalignment of the spinous processes, with large interspinous space, all combine to make certain the diagnosis of a jumped articular process and demonstrates conclusively the impossibility of safely reducing such dislocation by manipulation.

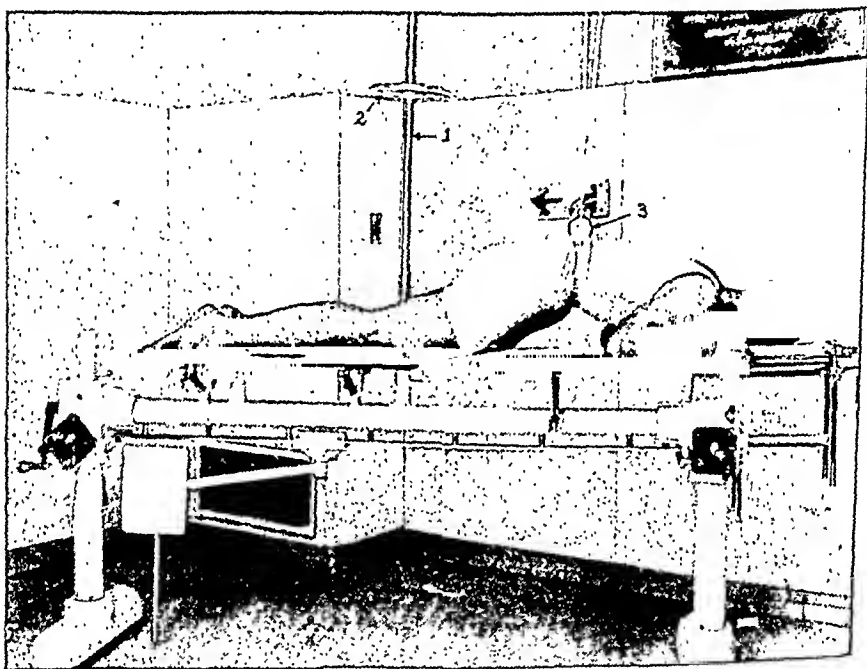


Fig. 8.—Setup for open reduction. Note (1) the telescoping post, (2) the gear to adjust the level and (3) the canvas sling placed at the level of the fracture-dislocation.

It is considered definitely hazardous to attempt any manipulation at all. The sequence of treatment believed to be best for this type of dislocation is as follows:

The patient is mounted on an operating table which breaks in the middle or on a special fracture table as in figure 8. The involved posterior vertebral arch is exposed by the subperiosteal method as in operation for fusion. The laminae and articular processes are exposed in detail. The table is then broken so as to induce the necessary flexion to disengage the jumped process. When the special table is used, a sling is placed transversely underneath the body at the fractured area and flexion is induced simply by elevating the suspension apparatus until the process has room for clearance. A bone forceps is then used to grasp the spinous process of the dislocated vertebra, or a blunt elevator is used to pry the process over. The operator then combines movements of posterior pull with rotation, the table is straightened away, the sling lowered and the dislocation thus rather easily reduced.

With the operative wound still open, the patient is hyperextended by foot suspension, and a lateral roentgenogram is taken in order to see that the centrum is fully restored to its vertical diameter. Obviously, no fusion is necessary in such cases. If, however, the posterior arch is otherwise damaged, fusion may be indicated.

Figure 9 illustrates another case. In this case the area of injury was not opened. The figure shows most of the features necessary to a diagnosis of dislocation of a posterior articular process. The roentgenogram made six months after fracture shows that the patient was saved from further gradual forward

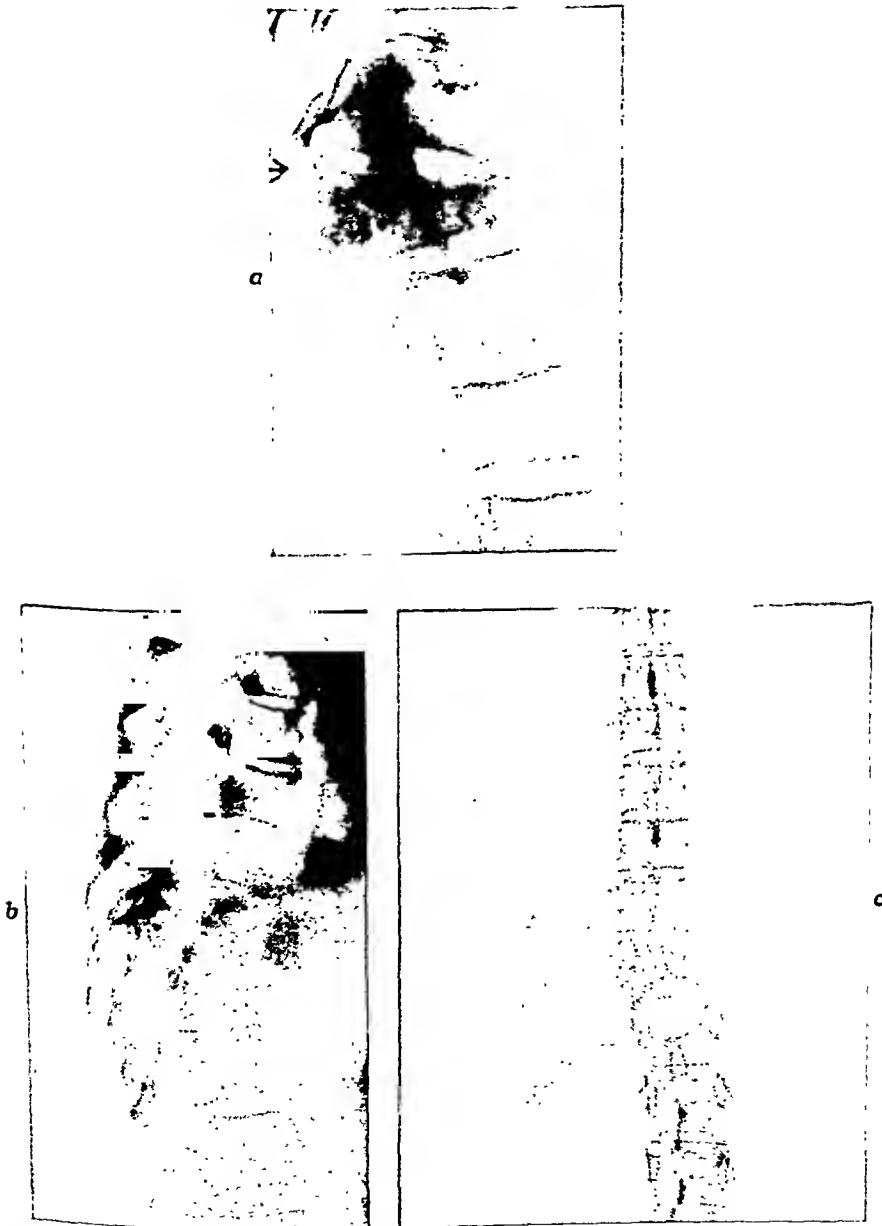


Fig. 9 (case M. P.).—(a) Fracture-dislocation without paralysis. Note the gross enlargement of the intervertebral foramen and the articular process caught on the apex of the process below, making closed manipulation futile. (b) Lateral view six months after the fracture, showing complete interruption of continuity in the posterior arch. Note the inability to exhibit detail of the articular process, the apparent bony bridge at the anterior portion of the body and the failure of reputedly strenuous attempts at hyperextension to decompress the centrum or to correct the angulation. (c) Anteroposterior view six months after the fracture. Note the lateral dislocation and the unequal compression as between the two sides.

dislocation by a bony bridge present between the two vertebrae in front. There is practically no evidence of continuity of structure of the posterior arch.

According to the history, a number of attempts were made to undo the deformity of the centrum by manipulation. Obviously, the centrum could not be opened to its complete height because of the block afforded by the jumped process posteriorly. It must be noted again that neither of the patients in these cases showed any neurologic signs. Obviously, attempts at manipulation in such cases are not only hazardous but futile.

#### TENSILE STRENGTH OF THE ANTERIOR LONGITUDINAL LIGAMENT

Since the determination of the tensile strength of the anterior longitudinal ligament of man on necropsy specimens demonstrated conclusively the surprising strength of the ligament, all manipulative work has been approached with greater confidence, and a modification of the Walton and Taylor technic for reducing cervical dislocations is justified.

In a paper published in 1938 the results of a series of tests of 7 ligaments obtained at necropsies were recorded. These ligaments were submitted to strains in a testing machine to determine stretch and breaking strength. The results demonstrated an average breaking point of 337 pounds (153 Kg.) with no evidence of stretch. Tests to determine the pounds of pull necessary to reduction showed 80 pounds (36 Kg.) to be sufficient in the cases requiring the most pull. The resulting safety factor is therefore in the ratio of 4 to 1. Except in cases of hyperextension injury or fracture-dislocation, complete assurance may be felt regarding the ability of the anterior longitudinal ligament to withstand the strain of both the initial injury and the reduction.

Descriptions of the Taylor technic for reducing bilateral dislocations of the cervical vertebrae all agree in principle but vary somewhat in detail. If one approaches a Taylor manipulation and visualizes the anterior longitudinal ligament and its known strength, the following modification of the technic seems obvious.

Were it not for this ligament, damage to the cord would undoubtedly ensue as the result of a longitudinal pull. Obviously, it would be a decided advantage to pull the head in flexion. Pulling in flexion, however, puts the maximum traction on the posterior roots of the cord. Therefore, it is decidedly unsafe to pull in flexion. Pulling longitudinally with extension would, in view of the check strap function of the anterior longitudinal ligament, provide a completely safe method of traction, but unfortunately the articular processes will not clear each other since the traction will be exerted principally on the anterior longitudinal ligament and the check strap effect of the ligament will preclude the possibility of a jumped process clearing the summit of the process below. Therefore, pull in the exact longitudinal axis of the body is highly important. A canvas sling placed around the operator's waist or buttocks and attached to the halter allows the operator the best mechanical advantage in handling the head (fig. 10). One hand is placed under the jaw, the other under the occiput, and one of the fingers of the occipital hand is then placed in contact with the cervical spine and its processes to determine crepitus. Ordinarily, distinct crepitus can be felt when the articular processes disengage. When this occurs with full traction still maintained on the head, the head is brought into extreme hyperextension. A lateral roentgenogram is then taken. If reduction has not taken place, another attempt, using more traction, should be made. It is interesting at this point to know how much one can pull without doing damage. Several persons were tested at this operative procedure, a spring balance being used. It was found that at the extreme

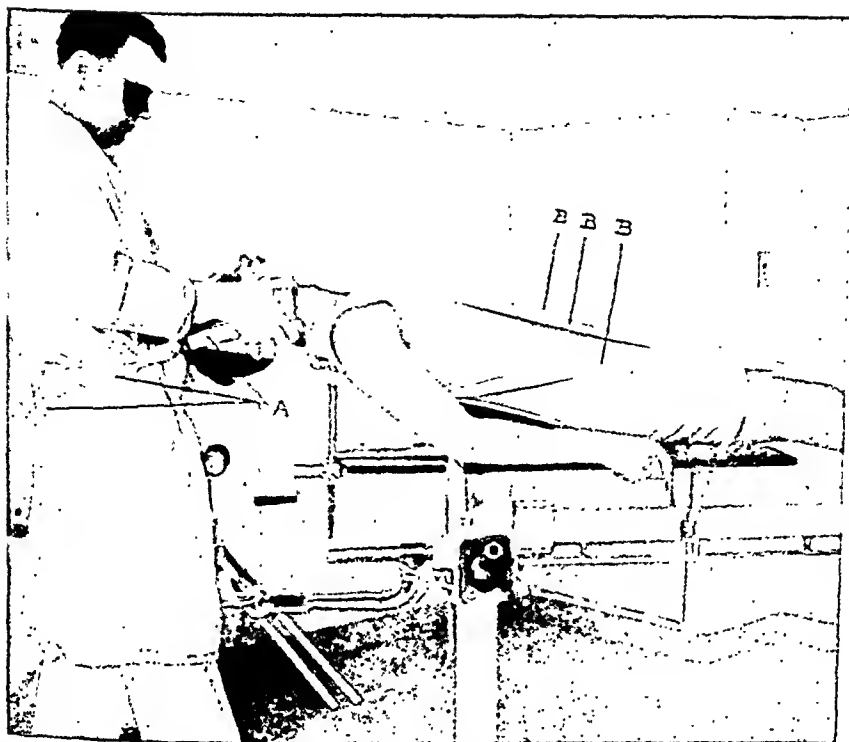


Fig. 10.—Method of applying a straight line pull for bilateral cervical dislocation. *A* indicates the halter purchase on the occiput and the chin. Note the band extending around the buttocks of the operator. *B, B, B* indicate countertraction bands that lash the shoulders to the perineal post. The operator's foot abuts against a stationary object on the floor for better purchase.

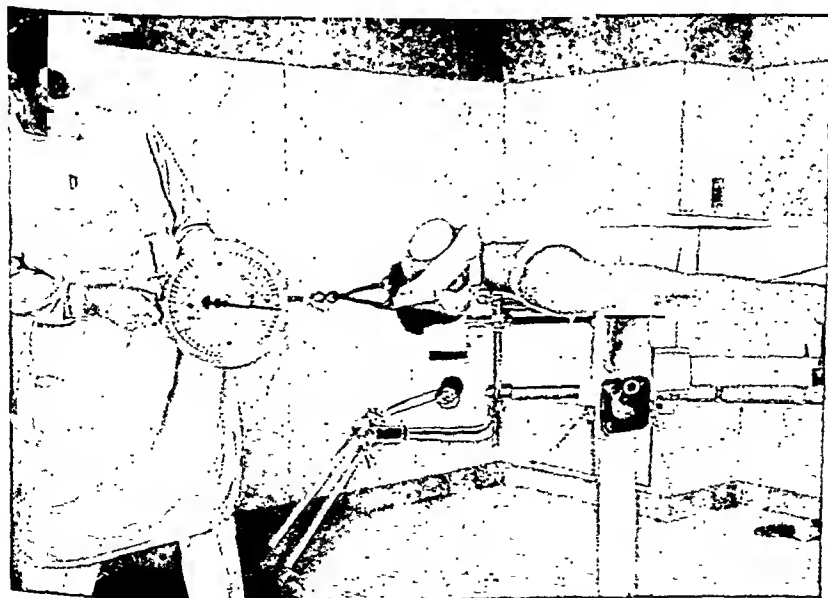


Fig. 11.—Interposed balance in the line of traction to find the traction strength of the operator in pounds. If this pull is done against the end of the table as a preliminary and the operator pulls to his utmost, the safety factor may be determined in advance.



of effort, the balance registered 80 to 125 pounds (36 to 56.5 Kg.) (fig. 11). Since the breaking point of the anterior longitudinal ligament is at weakest 160 pounds (72.5 Kg.) and the average breaking point is 337 pounds (153 Kg.), it is obvious that pulling the utmost in the standing position as illustrated will not tear the ligament or otherwise disrupt the cord or the nerve roots, provided the traction is in a straight line involving no flexion, extension or lateral deviation. Likewise, I have seen large amounts of weight used in connection with the Crutchfield tongs without damage. As much as 45 pounds (20.5 Kg.) has been applied to the skull continuously for days on end without discomfort to the patient. It is clear, however, that such a large amount of weight cannot be expected to serve a useful purpose because of the unyielding nature of the ligament. The anterior longitudinal ligament is completely inelastic. Determinations of stretch were made at the same time that the breaking point was determined. These tests were conducted in the same manner as in testing steel. During the increase in strain induced by the testing machine, the distance between two points, one above and one below a vertebral body was measured at increases of 50 pounds (22.5 Kg.) up to 150 pounds (68 Kg.) of weight imposed; no increase of separation was noted. These determinations of stretch seem completely critical since if there had been elastic yield in the ligament, pulling in the longitudinal axis or in hyperextension would carry the penalty of damage of the roots.

#### CERVICAL LUXATION

The analysis and manner of recognition and the treatment of a hitherto unrecorded but regularly occurring entity are herewith described. It is apparent from the histories of a number of patients that they suffered a severe injury, such as an automobile whip lash, usually some time prior to their first visit to a physician, with painful symptoms referable to the cervical portion of the spinal column. Roentgenograms of the involved regions fail to show definite evidence of forward dislocation of the body of a cervical vertebra.

There may be just sufficient luxation forward to suggest the possibility of slight displacement of the magnitude of a sixteenth of an inch or more as one looks at the anterior line of the body of the vertebra. The significant observation, however, in regard to the lateral picture is that the cervical portion of the spinal column has lost its normal anterior curve, and there usually is the slightest suggestion of anterior angulation at the level of an intervertebral space (fig. 12). It is well known that vertebrae have been completely dislocated in the cervical region, sufficiently to sever the cord, and reduced spontaneously by the patient's involuntary extensor recoil. It is assumed in these cases that a sufficient forward throw has occurred to sever the ligaments surrounding the posterior articular processes, that spontaneous replacement took place with the recoil but that the tear in the ligaments did not repair itself in the short position because no treatment was instituted. Subsequently, because of the incomplete repair of the ligamentous tear, the vertebra, under the weight of the head, gradually undergoes luxation forward. While the diagnosis and the proofs in such cases are not conclusive, it is safe to assume that the dislocation outlined has occurred and that immediate recognition of it and splintage with a collar to the hyperextended cervical portion of the spinal column are imperative to prevent gradually increasing luxation forward, which in a period of years would be sufficient to cause pain in the roots and traumatic arthritis in the intervertebral joints requiring eventual fusion to eliminate the painful disability. Several persons with a complaint of the latter kind have been seen years afterward, all of whom gave a definite history

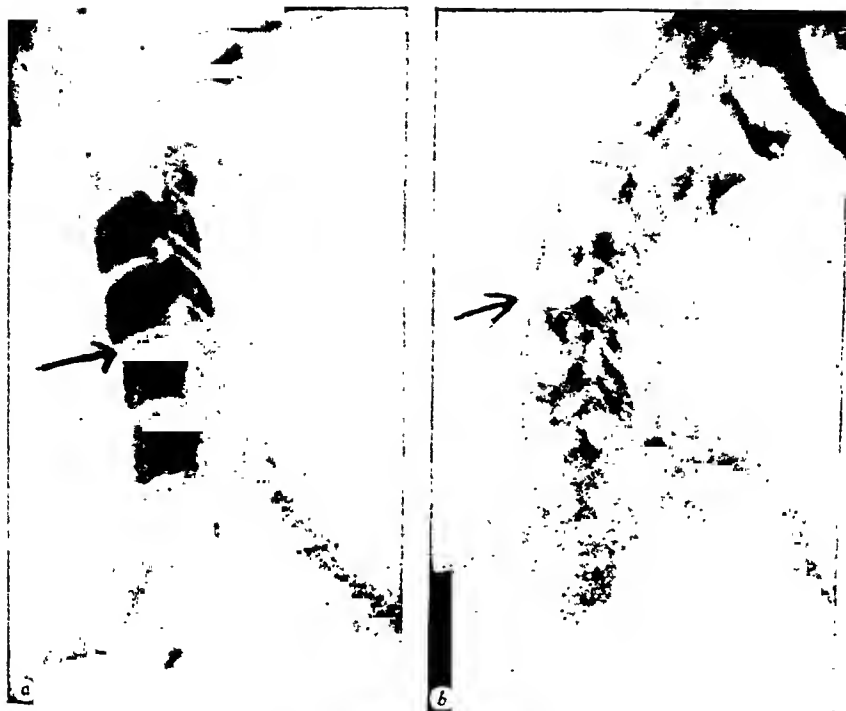


Fig. 12 (case M. M.).—(a) Typical partial dislocation of the cervical part of the spinal column. An arrow points to a slight forward displacement of the body of the fourth vertebra. Note the elimination of the normal cervical forward curvature. (b) Schanz collar in place. The normal symmetric cervical curve is exaggerated (hyperextended). The discrepancy at the fourth intervertebral space has been eliminated.

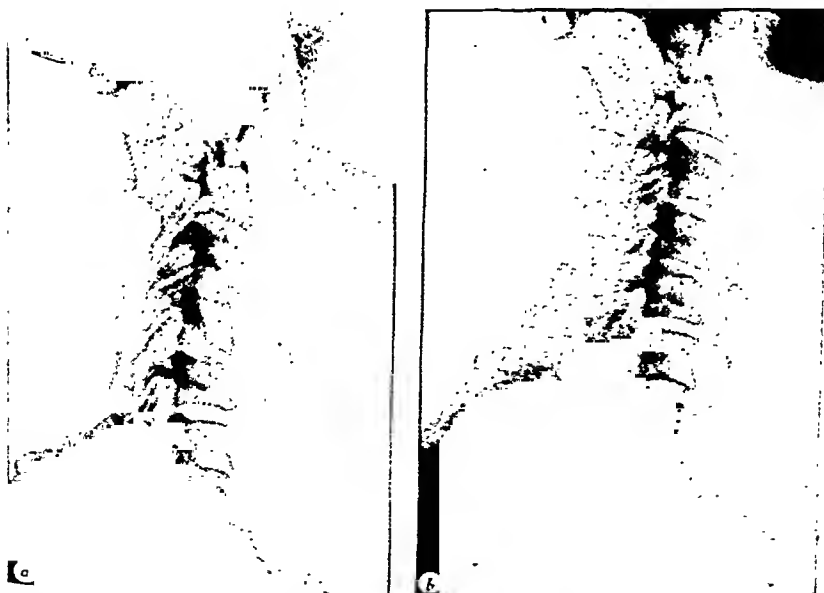


Fig. 13 (case J. K.).—(a) Long-standing partial forward dislocation of the third on the fourth cervical vertebra. Note the elimination of the normal cervical forward curve. (b) Post-operative fusion. The third, fourth and fifth vertebrae are fused to eliminate painful disability.

of a severe accident but whose symptoms at the beginning apparently did not merit roentgenographic investigation.

A case in point is that of a luxated cervical vertebra of several years' duration which was fused recently, with complete disappearance of pain due to spinal root pressure (fig. 13).

A sufficient number of these cases have not yet been reported to enable one to arrive at definite conclusions. Enough, however, have occurred so that any case presenting a history of a recent or even somewhat remote severe accident, particularly of the automobile type, and a complaint of pain in the neck should never escape roentgenographic investigation. If the lateral plate shows elimination of the cervical forward curve, this alone constitutes an anatomic change which not only requires explanation but is best explained by the mechanism described. If the patient comes for examination early, he is immediately fitted with a hyperextension collar not only restoring but exaggerating the normal anterior curvature for the time being. Such patients recover completely without operation. The collar obviously must be worn for several weeks to months.

Since this observation was made several years ago, such cases of progressive cervical luxation have become considerably more numerous. It therefore can definitely be said that this type of lesion is a clinical entity. This demonstration also points to the necessity of awareness on the part of members of the medical profession generally that all cervical injuries must be analyzed roentgenographically and of becoming accustomed to diagnosing by inference, starting with the fact that there normally is an anterior curvature of the cervical part of the spinal column and arriving at the almost inescapable conclusion that rupture of the posterior ligamentous investiture has taken place and that, the posterior ligaments having once given way, normal unguarded movements of the head will induce a progressive lesion which will later become manifest as a dislocation easily recognizable in the roentgenogram. By this time painful symptoms have so increased that fusion of two to four of the cervical vertebrae is necessary to eliminate pain.

# OSTEOCHONDRITIS DISSECANS

## A DISCUSSION OF TWO SIMILAR LESIONS

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Osteochondritis dissecans is an aseptic necrosis of subchondral bone and the overlying cartilage. This lesion is seen most frequently in young men. The most common site affected is the knee joint, with involvement of the medial femoral condyle and occasionally of the patella. The elbow is a frequent site, with the capitellum the most common area involved.

Trauma is considered the inciting cause for the development of this condition. Some consider that there may be a developmental or congenital background.

A condition noted in older persons resembles this lesion in some respects. It also has been described by some writers as osteochondritis dissecans. I have noted it on the medial femoral condyle in adults who required surgical treatment for a fracture of the internal meniscus. I have noted its occurrence also among persons who showed an acutely painful knee after injury to a knee joint revealing mild hypertrophic arthritis. I have also seen it involving the patella in patients who had an old injury to the patella. The lesion macroscopically consists of an erosion and fibrillation of the articular cartilage, with eburnation of the subchondral bone. Specimens taken from these areas reveal degenerated cartilage and avascular subchondral bone. Sometimes the cartilage is found to have broken loose into the joint. These fragments show, on microscopic examination, subchondral bone attached to fibrillated cartilage. In no instance have I seen this condition associated with osteochondromatosis.

The diagnosis of osteochondritis dissecans is partially dependent on an accurate roentgen examination. This is frequently found to be even more helpful than the clinical findings in making a positive diagnosis. The clinical aspects of osteochondritis dissecans can be rarely differentiated from those of a rupture of the internal meniscus when the lesion occurs in the knee. When it occurs in other joints, the diagnosis may be easier. I wish to point out the importance of careful roentgen examination as a most valuable aid in the correct diagnosis of osteochondritis dissecans. In the case illustrated by figure 1 the condition occurred bilaterally in the knees. The patient presented symptoms referable only to one joint. He was 23 years old, and could give no history of an injury to the supposedly normal knee. The symptomatic knee had been injured one year prior to the taking of these roentgenograms. At that time he had severely twisted it while at work. Following this injury, he had had constant complaints, with locking and swelling, associated with pain, as the most persistent symptoms. The presence of a similar condition in the opposite knee, without separation of the fragments, suggests that this lesion may be due to developmental changes or may have a congenital background. The roentgenograms of the other 2 cases (figs. 2 and 3) demonstrate the visualization of osteochondritis dissecans involving an ankle and the head of a femur without detachment of the fragments. Figure 2 reveals osteochondritis dissecans of an astragalus, which was first seen after the patient had suffered a severe sprain of the ankle. Figure 3 shows a similar lesion occurring in the head of a femur. The condition was first noted about a year after the patient had

received a fracture of the acetabulum, directly above the lesion in the head of the femur. Roentgenograms taken at the time of the fracture revealed no evidence of the osteochondritis dissecans.

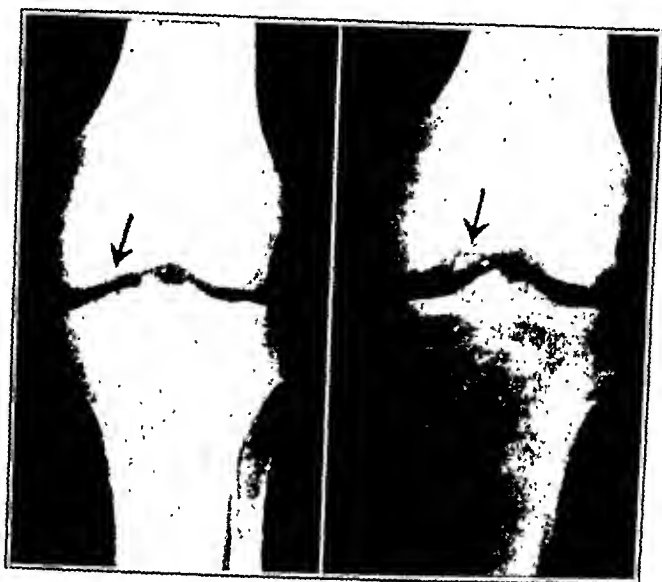


Fig. 1.—Osteochondritis dissecans of both knees of a patient who experienced symptoms from only one knee joint, for which he gave a history of injury.



Fig. 2.—Osteochondritis dissecans of the astragalus.

These 3 cases are instances of a lesion involving the articular cartilage and the subchondral bone. Trauma seems to be at least one of the etiologic factors. Whether the condition noted in the supposedly uninjured knee of the case illustrated by figure 1 was the result of unrecognized trauma is not known. Whether the changes noted in conjunction with other injuries to joints, as in the case in

which the patient revealed fibrillating cartilage of the medial condyle of the femur with underlying ebulation of the subchondral bone associated with a fractured internal meniscus, are properly classified under this title is not clear. The underlying factors seem to be the same, namely, aseptic necrosis with involvement of cartilage and subchondral bone. The clinical picture is not the same in most instances. Locking is not a common complaint in cases of the latter type, and the diagnosis is usually clouded by the complaints associated with the primary condition requiring care. The name "osteochochondritis dissecans" fits the charac-

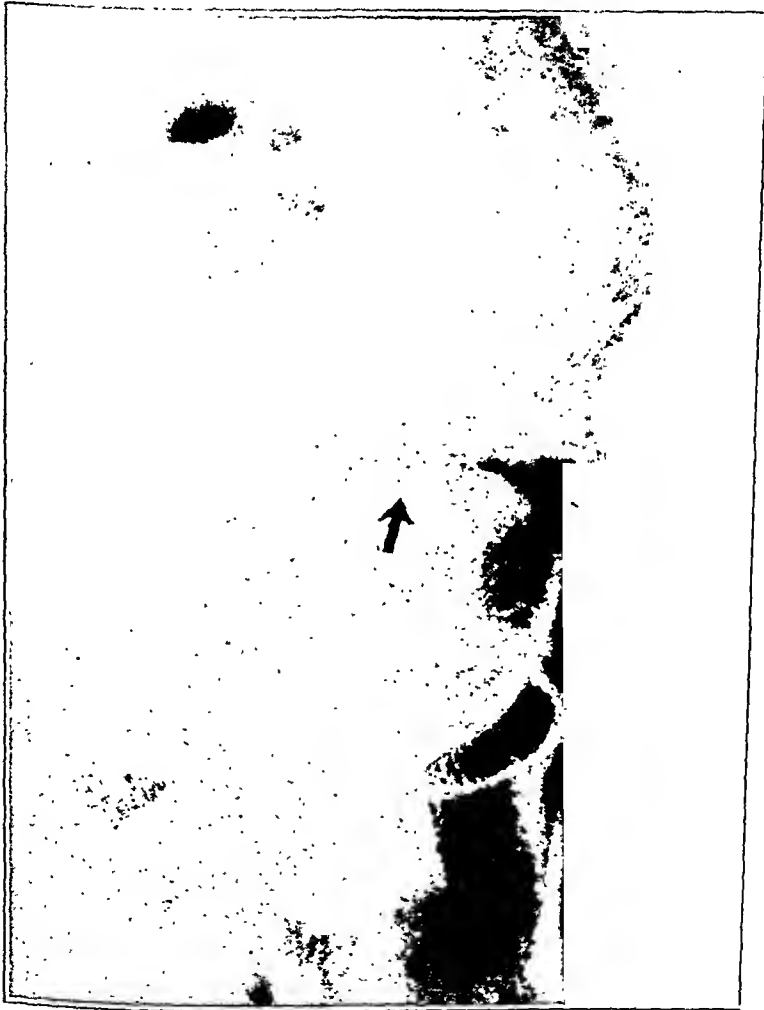


Fig. 3.—Osteochondritis dissecans occurring in the head of a femur.

teristics in both lesions. However, the other lesions described seem to fit more accurately into the category of lesions associated with hypertrophic arthritis and may well be described as degenerative osteochondritis dissecans. They are not as well walled off and circumscribed in character as those visualized in the roentgenograms and are most commonly associated with some primary change in the joint. The roentgenographic changes are quite different.

As to treatment of the two types of lesions described under this title, my associates and I have found that the therapy for degenerative osteochondritis dissecans is identical with that for true osteochondritis dissecans. In both instances

the articular surface has to be thoroughly smoothed off, the loose fragments taken out and the overhanging shelves removed. The response to this type of treatment in the one condition is also very similar to the response in the other. The relief of pain and discomfort in both instances is quite apparent.

In discussing osteochondritis dissecans I have given as examples 3 classic cases, in one of which the disease was bilateral. The importance of accurate roentgen examination in making a correct diagnosis cannot be overemphasized. I have pointed out the similarity of this lesion to the frequently noted lesion involving the internal condyle of the femur and the patella in patients who have required surgical treatment for fracture of the internal meniscus, old injury of the patella and hypertrophic arthritis. I have preferred to classify lesions of the latter type under the title of degenerative osteochondritis dissecans. The differential findings between these similar types, as well as the common findings, have been discussed in order to reveal more clearly why I consider these two types of osteochondritis dissecans as representing similar responses to different etiologic factors.

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# PSEUDARTHROSIS AND NEUROFIBROMATOSIS

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AND

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Although pseudarthrosis has been described in association with neurofibromatosis, the mechanism by which it arises has not been explained.<sup>1</sup> It is our purpose to report a case of congenital bow leg and pseudarthrosis of the tibia and the fibula associated with neurofibromatosis in which studies have assisted in clarifying the genesis of pseudarthrosis and localized lesions of bone in this condition. The history, the surgical treatment and the pathologic observations are reported in detail.

## REPORT OF A CASE

I. D., a girl aged 6 years 11 months, was admitted to the Children's Hospital on May 14, 1940, complaining of a tender swelling in the right arm and a deformity of the right leg. A lump in the right arm was noted eight months prior to admission. It had increased slightly in size since the original observation, and although it did not interfere with the use of the arm, it was quite sensitive to pressure.

The bowing of the right leg had been present since birth and, except for the deformity, had caused no symptoms. The mother was of the opinion that the degree of deformity had not changed over the years. There was no history of trauma, and at no time had there been any complaint of discomfort. The other details of the history obtained were not considered pertinent to this presentation except that the father had small café au lait spots on his skin.

*Physical Examination.*—The child was rather undersized and undernourished. Her skin showed multiple areas of brownish pigmentation, so-called café au lait spots (fig. 1). Her head was markedly dolichocephalic in type and her jaw was prognathic. Her posture was poor, with increased lordosis, protruding abdomen and round shoulders. There was no beading of the ribs or Harrison's groove. Otherwise the examination was not significant except for findings in the right arm and the right lower extremity.

Palpation of the lateral aspect of the right arm at the juncture of the lower and the middle third revealed a tender firm nodular mass beneath the subcutaneous tissue, the main portion of which was about 3 cm. long and 0.6 cm. in diameter.

The right leg showed increased knock knee with anterolateral bowing of the tibia. The left leg was entirely normal, and the lower extremities were equal in length.

Roentgenograms of the right leg taken at the time of admission (fig. 2) revealed an ununited oblique fracture in the distal portion of the fibula, which had evidently been present for some time, and a sinuous bowing of the tibia, most marked in an anterolateral direction. The tibia showed an irregular thickening of the cortex, which was maximal at the level of bowing, but no localized defects could be seen in the bone at this time. Roentgenograms of the remainder of the skeleton showed no significant abnormalities. However, a review of

From the departments of orthopedic surgery and pathology of the Children's Hospital and the Harvard Medical School.

1. (a) Stalmann, A.: Nerven-, Haut- und Knochenveränderungen bei der Neurofibromatosis Recklinghausen und ihre entstehungsgeschichtlichen Zusammenhänge, Virchows Arch. f. path. Anat. 289:96, 1933. (b) Ducroquet, R.: A propos des pseudarthroses et inflexions congenitales du tibia, Mém. Acad. de chir. 63:863, 1937. (c) Ducroquet, R., and Cottard, A.: Pseudarthrose congenitale de jambe. Deformation osseuse de la neurofibromatose, J. de chir. 53:483, 1939. (d) Barber, C. G.: Congenital Bowing and Pseudarthrosis of the Lower Leg: Manifestations of von Recklinghausen's Neurofibromatosis, Surg., Gynec. & Obst. 69:618, 1939. (e) Moore, B. H.: Some Orthopaedic Relationships of Neurofibromatosis, J. Bone & Joint Surg. 23:109, 1941.



roentgenograms which had been made elsewhere two years previously revealed that the fracture of the fibula was not present then, although the appearance of the tibia and the fibula was otherwise similar to that seen in the more recent films.

Laboratory examinations on admission showed no particular abnormalities. The values of blood calcium and phosphorus were 9.9 mg. and 5 mg. per hundred centimeters, and the value of phosphatase was 9.3 Bodansky units. An intradermal test with tuberculin in the dilution of 1:1,000 was negative, as was the Hinton test for syphilis. The blood cell counts were normal, as were the findings in the urine.

*First Operative Procedure.*—On May 27 the mass in the right arm was exposed and found to be a wormlike nodular whitish tumor, which was attached to the radial nerve and in part had to be dissected from it. There were many continuations from the main mass into

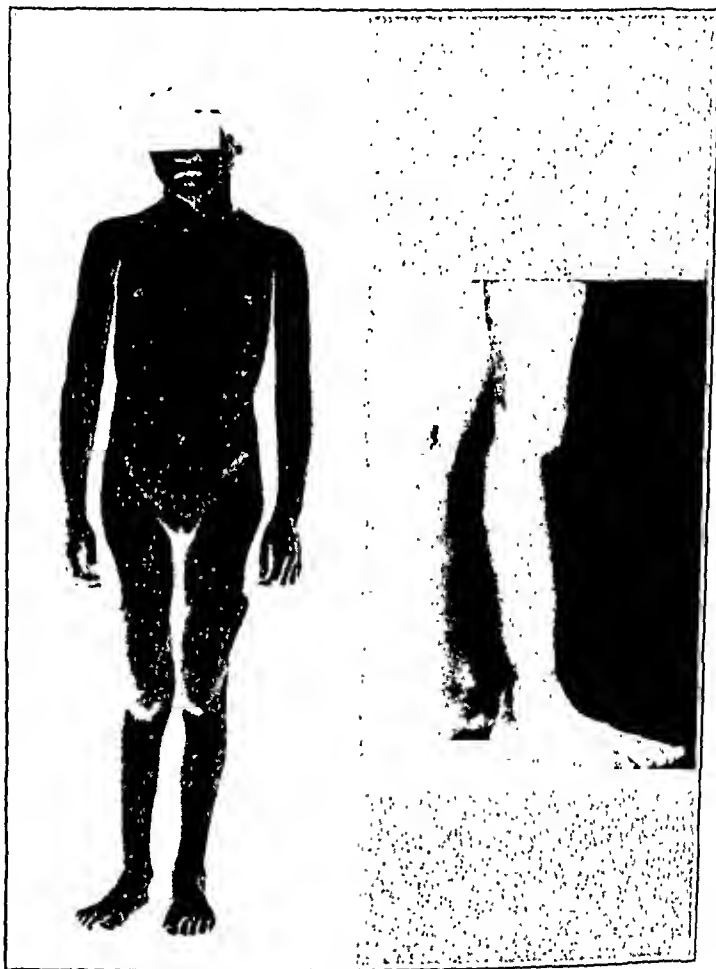


Fig. 1.—Photographs taken in May 1940 when the patient was first admitted to the Children's Hospital, at the age of 7 years. Note the pigmented patches on the trunk and the antrolateral bowing of the right leg.

the fascia and muscles, although bone and periosteum were not involved. All recognizable tumor tissue was excised.

An incision was then made over the distal third of the right leg so as to expose the tibia at the site of maximal cortical thickening and the fibula in the area of the defect which was visible in the roentgenograms. About 5 cm. above the lateral malleolus, the periosteum over the fibula was found thickened and the underlying bone was bulbous. Incision of the periosteum exposed a definite area of nonunion, from which a rectangular block of bone was removed so as to give a representative longitudinal section of the area. Following this, a section of bone for microscopic examination was removed from the tibia at the site of the greatest cortical thickening. The leg was immobilized in a plaster splint from the toes to the groin, with the knee flexed at about 45 degrees.

*Pathologic Examination of the Tissues Obtained at the First Operation.*—The material excised from the right arm was a serpentine mass of thickened nerves. Microscopic examination showed the nerve bundles to be thickened by a proliferation of loosely arranged elongated spindle-shaped cells; a picture typical of plexiform neurofibroma (fig. 3).

The block of bone and attached periosteum removed from the region of the ununited fracture of the fibula displayed a freely movable line of dense soft tissue 2 to 3 mm. wide. This zone corresponded to the fracture line seen in the roentgenograms.

On microscopic examination the fracture fragments were seen to be separated by a vascular cellular tissue composed of streaming bundles of elongated cells with little or no intervening collagen. The nuclei in some areas showed a tendency to form parallel rows or "palisades" (figs. 4 and 5). Osteoblastic activity and osteoid formation were evident along the margins of the fracture fragments, and in this region there was an intermingling of the described cellular tissue with fibrous and osteoid tissues. This intermingling of the soft cellular tissue with the osteoid material produced a defective type of osteoid, poorly calcified.



Fig. 2.—Roentgenograms of the right leg in the anteroposterior and lateral views taken at the time of the first admission, May 14, 1940, show the anterior and lateral bowing of the tibia, with thickening of the cortex, and the ununited fracture of the fibula.

There were areas of a more cartilaginous type of callus in which there was a tendency for the tissues to disintegrate with formation of eosinophilic debris. In these areas osteoclastic giant cells were numerous.

The bone at a little distance from the fracture line was entirely normal. The periosteum did not contain any cellular tissue of the type that was found between the fracture fragments. The pathologic diagnosis was intraosseous neurofibroma of the fibula with pathologic fracture and pseudarthrosis.

The specimen taken from the right tibia was found on microscopic examination to consist of cortical bone which was not unusual except for slight enlargement of the haversian canals. The connective tissue within the canals was quite vascular and showed no neoplastic change or other abnormality. The overlying periosteum was not abnormal. The diagnosis was cortical thickening of the tibia with enlarged haversian canals.

*Course in the Interval Before the Second Admission.*—When the splint which had been applied at the first operation was removed, Sept. 5, 1940, fourteen and one-half weeks after the operation, there was still no roentgenographic evidence of union of the fibula, although the defect in the tibia created by the removal of the block for microscopic examination had healed.

Roentgenograms taken on September 19 showed a new rounded defect in the tibia, distal to the site of the previous removal of a section of bone and opposite the site of nonunion in the fibula (fig. 6). This was interpreted as probably a neurofibroma of bone. It was decided that no intervention should be made at this time, but that the defect should be observed.

*Second Admission to the Hospital.*—On December 14, seven months after the previous admission to the hospital, the patient was readmitted, with the story that eight days before,



Fig. 3.—Photomicrograph ( $\times 120$ ) of a section of the plexiform neurofibroma removed from the right arm. Two small nerve bundles and a part of a larger one are shown enlarged by the proliferation of loosely arranged neurofibroma tissue. Nuclear palisading is slight. Nerve fibers persist in the centers of the bundles.

while playing in the snow, she fell and injured her right leg. She was taken to a nearby hospital, where an unsuccessful attempt was made to reduce a fracture of the right tibia and fibula. She was then transferred to this hospital with her leg immobilized in a plaster splint. Roentgenographic examination showed a transverse fracture of the tibia at the juncture of the distal two thirds and proximal one third, with a new fracture of the fibula at this same level (fig. 7). The tibia had been fractured approximately through the area of previous removal of bone for biopsy, although no gross defect from this procedure was visible in the roentgenograms. The line of fracture did not involve the defect in the tibia which had been recognized at the last roentgenographic examination and interpreted as a neurofibroma of bone. Attempts

at closed reduction of this fracture were unsuccessful in that, although the fracture could be reduced, the surfaces seemed to be smooth and could not be locked in position.

*Second Operation.*—Open reduction of the fracture with biopsy of the defect of the tibia was performed on December 23. There seemed to be a small amount of fresh subperiosteal callus at the site of fracture and some similar tissue between the fragments. This was resected down to healthy-appearing bone, and the fracture was fixed with a four screw vitallium plate. Following this, the defect in the tibia distal to the fracture was exposed. The tissue in this area in its gross aspect resembled granulation tissue in many particulars and was separated from the periosteum by a thin layer of cortical bone. It was resected for histologic examination.

*Pathologic Examination of Tissues Obtained at the Second Operation.*—The soft tissue nodule removed at the site of the roentgenographic defect and the material from the site of



Fig. 4.—Photomicrograph ( $\times 81$ ) of a section taken through the ununited fracture of the fibula. A broad central zone of vascular tissue lies between the adjacent fracture ends. Numerous thin-walled blood channels are present. Osteoclastic type giant cells are seen at the upper right; osteoblastic activity and osteoid formation are seen at the upper center and lower right.

nonunion both showed a histologic picture entirely similar to that seen in the tissue from the area of nonunion in the fibula previously described (fig. 8A and B). The diagnosis was (1) neurofibroma of bone and (2) pathologic fracture of the tibia with neurofibroma of bone.

*Course in the Interval Before the Third Admission.*—The extremity was immobilized in a plaster splint, which was not removed until April 9, 1941, approximately three and one-half months after the operation. At this time union was solid and there was definite callus with obliteration of the fracture line.

*Third Admission to the Hospital.*—This girl was again admitted on June 5, 1941 with the story that ten days before this she had stumbled over a cobblestone, with immediate

pain in her right leg. The trauma was minimal. She was able to walk, but the leg became swollen and painful.

Examination showed tenderness in the distal portion of the tibia, below the site of the former fracture. Roentgenographic examination showed a transverse fracture of the tibia, distal to the previous fracture, at the site of the most recent removal of tissue for biopsy, although the defect created at that time had almost completely healed (fig. 9). There were, however, a few new defects anteriorly just below the fracture line. There was no displacement, and the extremity was immobilized in a plaster splint for seven weeks. Since at the end of this time there was no evidence of union, and definite defects in the bone adjacent to the line of fracture existed, an open procedure was performed.

*Third Operation.*—On July 29 an incision was made in a longitudinal direction over the distal third of the tibia, excising the scar of the previous operation in this area. The vitallium plate which was used in the immobilization of the previous fracture was removed. Union was solid in this area, and no abnormal tissue was noted. The site of the recent fracture

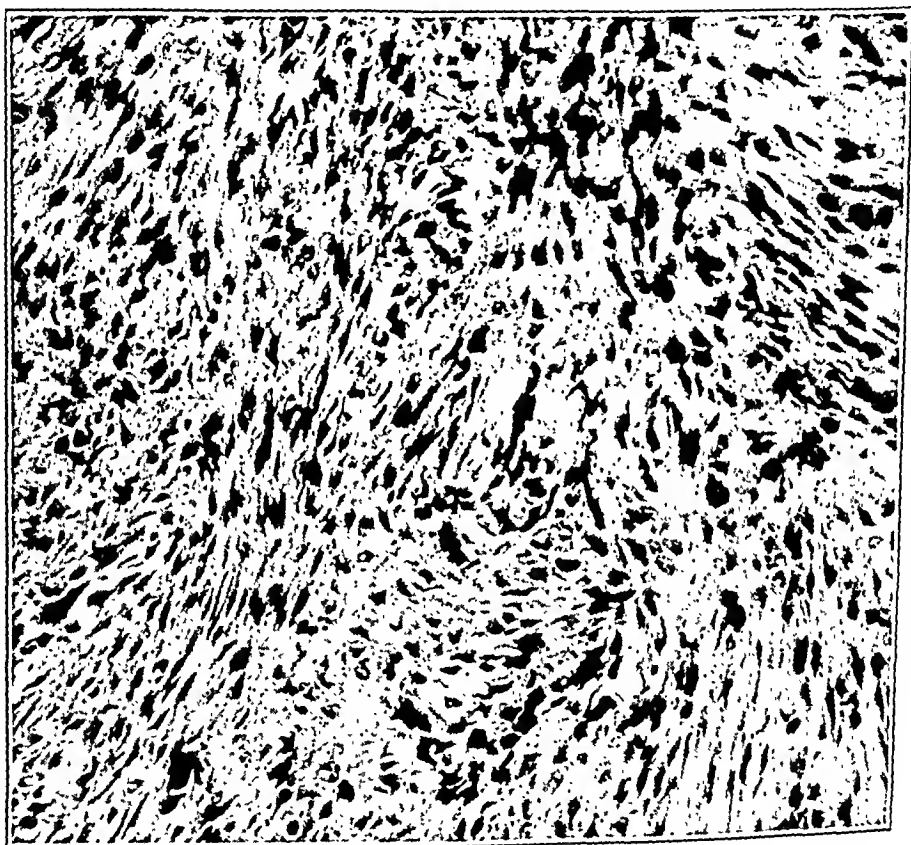


Fig. 5.—A higher power photomicrograph ( $\times 250$ ) of the tissue in figure 4. The streaming, swirling, interlacing bundles cut in various planes and the nuclear palisading are characteristic of neurofibroma.

was then exposed. There was no evidence of union. The bone adjacent to the line of fracture in the tibia was resected, as was the area of nonunion in the fibula. The resected portion of the tibia contained certain defects occupied by tissue of fibrous type. The surfaces of the tibia were coapted and plated in position. The distal fragment of the tibia was very atrophic and friable. The use of a large bone graft was considered, but deferred at this time; small osteoperiosteal grafts were placed across the line of fracture. The extremity was immobilized by means of a circular plaster splint extending from the toes to the groin.

*Pathologic Examination of the Tissue Removed at the Third Operation.*—The tissue was similar to that seen in previous sections. The histopathologic diagnosis was recurrent neurofibroma of bone with pathologic fracture.

*Fourth Admission to the Hospital.*—Roentgenograms of December 15 (fig. 10A) showed the bone plate to be holding the fragments in good position, but there was no evidence of

union; in fact, there was absorption of bone from the adjacent surfaces. The patient was then allowed partial weight bearing, a modified Boehler walking iron being used. The absorption of bone from the adjacent fragments which was in evidence in the roentgenograms of December 15 increased markedly, and the patient was readmitted to the hospital on May 16, 1942. The roentgen picture at this time was typical of pseudarthrosis of the tibia.

*Fourth Operation.*—On June 25 the vitallium plate, which had broken, was removed, the tissue occupying the fracture line, which was of gray glistening character, was widely excised, and two large bone grafts removed from the opposite tibia were inserted in onlay fashion with fixation by vitallium screws after the technique used by Boyd.<sup>2</sup>

*Pathologic Examination of the Tissue Removed at the Fourth Operation.*—Again, histologic examination of tissue from the site of nonunion led to the diagnosis of recurrent neurofibroma of bone.

On October 15 roentgenograms of the tibia showed solid union (fig. 10 B).



Fig. 6.—Roentgenograms, oblique and lateral views, made on Sept. 19, 1940, sixteen weeks after the first operative procedure. The fracture of the fibula is still ununited, although a small amount of callus has formed. The biopsy defect in the tibia is almost obliterated, although the bone in this region is more dense. The small rounded defect in the tibia is seen for the first time. Note its position well below the site of the removal of bone for biopsy.

#### COMMENT

The case under consideration presented bowing and pathologic fractures of the tibia, as well as pseudarthrosis of the fibula, in association with neurofibromatosis. The extraosseous manifestations of the neurofibromatosis included numerous café au lait spots on the skin and a plexiform neuroma involving the radial nerve.

Although pseudarthrosis has been noted as associated with neurofibromatosis in certain instances, the actual mechanism by which it occurs has not been demon-

2. Boyd, H. B.: Congenital Pseudarthrosis: Treatment by Dual Bone Grafts, *J. Bone & Joint Surg.* **23**:497, 1941.

strated. Moore<sup>10</sup> stated: "We believe that the condition of the nerve and the pseudarthrosis stand in the relationship of cause and effect, though the mechanism of the production is not clear." In none of the reported cases of pseudarthrosis associated with generalized neurofibromatosis have we been able to find a microscopic description of the tissue from the area of pseudarthrosis.

In our case the pseudarthrosis seems to be associated directly with intraosseous neurofibromas which caused pathologic fractures of the tibia and the fibula and retarded or prevented bony union. The rounded defect in the tibia is interpreted as an example of the first step in the process, that is, the development of a neurofibroma within the bone (fig. 6). The evidence suggests that the ununited fracture of the lower end of the fibula had been preceded by the formation of a similar defect. This

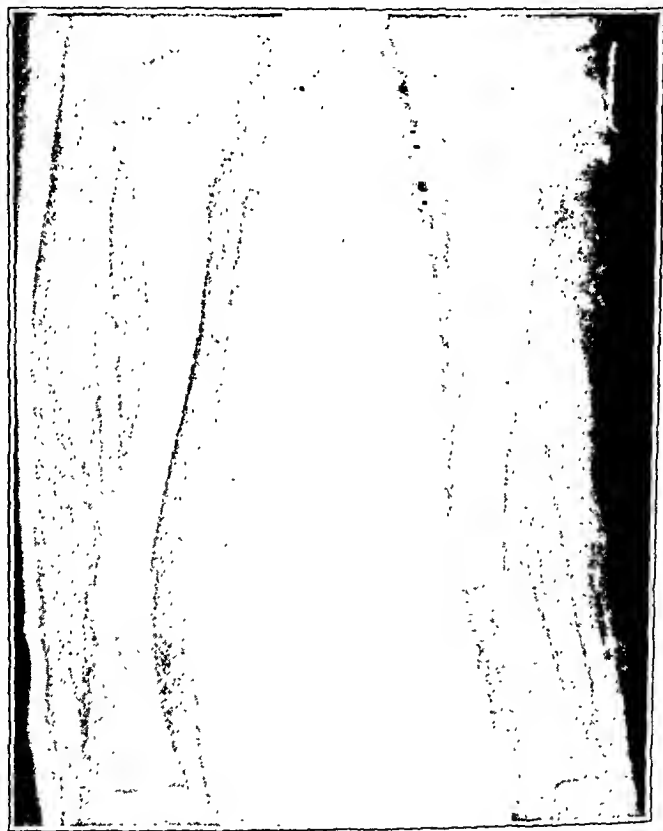


Fig. 7.—Anteroposterior and lateral views of the leg in a plaster splint, made Dec. 14, 1940, when the patient was readmitted to the hospital. There is a rather smooth transverse fracture of the tibia at the level of the site of removal of the biopsy specimen. Just below this level there is a new fracture of the fibula. The old fracture of the fibula remains ununited. The rounded defect in the tibia, noted previously (fig. 6), is somewhat larger.

fracture was caused by trauma so slight as to escape the notice of the patient. The failure of the fibula to unite was due to the presence of neurofibromatous tissue between the fracture fragments.

The first fracture of the tibia occurred in an area where tissue had been removed for biopsy. Exploration of this fracture seventeen days after its occurrence demonstrated the presence of neurofibroma between the bone ends. After excision of this tissue with open reduction of the fracture and immobilization by internal fixation, this fracture united satisfactorily.

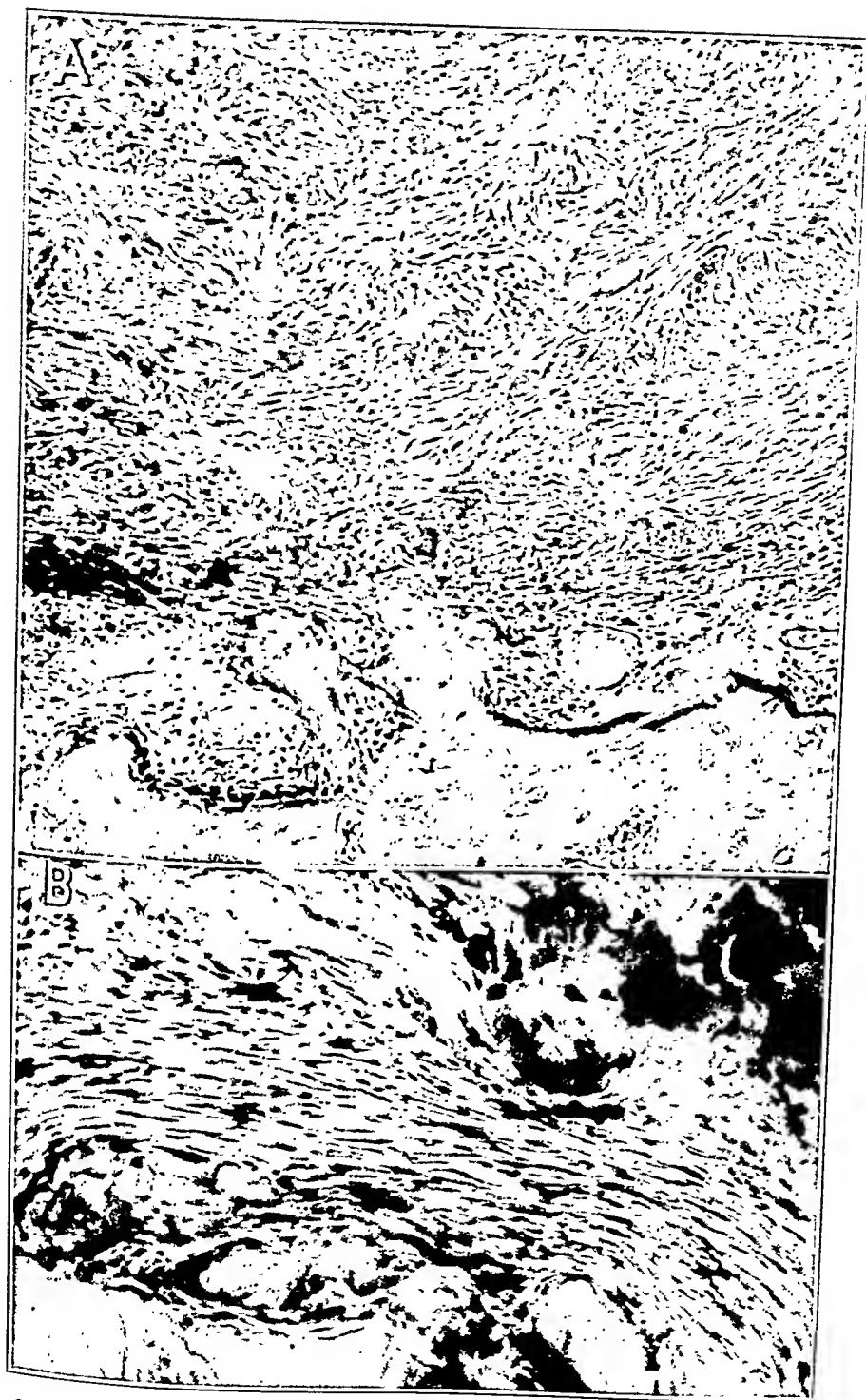


Fig. 8.—*A*, photomicrograph ( $\times 170$ ) of a section made through the soft tissue nodule occupying the small rounded defect in the tibia (fig. 6). The tissue is similar to that found in the area of pseudarthrosis of the fibula (fig. 5). Note the distinction between the tumor tissue and the adjacent intertrabecular connective tissue. The surrounding bone shows osteoblastic activity and the formation of normal new bone tissue. *B*, photomicrograph ( $\times 250$ ) of tissue obtained from the margin of the first fracture of the tibia, seventeen days after the fracture occurred. A streaming bundle of neurofibroma tissue occupies the site of fracture.



The second fracture of the tibia occurred in an area where neurofibromatous tissue had been demonstrated histologically prior to the fracture. This fracture, as all the others, occurred with little trauma and is attributed to the persistence and growth of the neurofibroma which had been incompletely excised at the time of the biopsy in this area. New defects in the bone at this level were demonstrable roentgenologically and at operation, when the second open reduction with plating was done.

This fracture failed to unite; there was increasing absorption of bone with fracture of the bone plate. The roentgen picture at this time was entirely typical of so-called pseudarthrosis of the tibia.



Fig. 9.—Anteroposterior and lateral views taken June 5, 1941, ten days after mild trauma. A new transverse fracture of the tibia is seen distal to the bone plate and at the site of the biopsy specimen of Dec. 23, 1940. The defect created by the operation is almost obliterated, but new defects are seen anteriorly just below the line of fracture. The fractures of December 1940 have healed.

Again exploration demonstrated the presence of recurrent neurofibroma. This was widely excised and fixation was secured by means of dual bone grafts (Boyd), with union following.

The tissue removed from the area of pseudarthrosis of the fibula and from the regions of pathologic fracture of the tibia was in many areas indistinguishable microscopically from that obtained at the biopsy of the localized osseous lesion which was unassociated with fracture. All showed a similar structure, consisting of streaming, swirling, interlacing bundles of elongated cells, with the nuclei tending to align themselves in rows or "palisades." Only a scant amount of collagen was distributed

between the cells and between the cell bundles. In the areas of fracture the adjacent bone showed definite ability to produce osteoid tissue, but the neurofibromatous tissue became intermingled and incorporated with it, resulting in a poorly calcified and defective type of osteoid tissue.

It was suggested in our case that the intraosseous neurofibromas developed from nerves within the bone rather than from those of the periosteum. The periosteum was singularly free of tumor tissue except in a single portion and that was the site of a recurrence of the tumor after a biopsy had been done in the area.



Fig. 10.—*A*, roentgenogram of Dec. 15, 1941, four and one-half months after the plating of the second fracture of the tibia shows absorption of bone from adjacent surfaces, with no evidence of union. *B*, roentgenogram of Oct. 15, 1942, taken approximately four months after dual bone grafts, shows healing of pseudarthrosis.

Even the localized tumor defect of the tibia (fig. 6), which the roentgenograms indicated was immediately beneath the periosteum, was found at operation to be separated from the latter by a small shell of cortical bone. This would suggest that the neurofibromatosis arose in intraosseous nerve tissue. That nerve tissue exists within the bone has been demonstrated by Stohr<sup>3</sup> and others. It is possible

3. Stohr, P.: Das periphere Wervensystem, in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie der Menschen, Berlin, Julius Springer, 1928, vol. 4, p. 419.

however, as proposed by Brooks and Lehman,<sup>4</sup> that the neurofibromas may arise from the nerves of the periosteum, erode into the bone and subsequently be covered by a shell of bone laid down by the periosteum, although this was not suggested by the findings in our case.

The cause of the bowing of the tibia is not readily apparent. We have seen several other patients with bowing of a similar character in association with neurofibromatosis. The discovery of tumor tissue in the shaft of the bone might lead one to speculate as to the possibility of the presence of neurofibroma at the zone of enchondral ossification, causing inequality of the rate of bone growth and consequent deformity. Under such circumstances, with progression of the growth zone away from the tumor, the normal rate of growth might be reestablished. No evidence to support this theory could be determined, as roentgenographically no definite defects in the tibia were demonstrated before the child was admitted to the hospital at the age of 7 years.

The findings in this case have led us to review the literature of "congenital pseudarthrosis," and although there is considerable speculation on the nature of the process, actual pathologic investigation has been relatively meager. In some instances of this condition "cysts" of the bone have been reported to have been demonstrated by roentgenograms prior to the occurrence of the fracture which led to the pseudarthrosis. These cases have been considered from the roentgenographic evidence as instances of a congenital form of localized osteitis fibrosa cystica.<sup>5</sup>

Wade<sup>6</sup> reported several cases of congenital pseudarthrosis of the tibia, in some of which there was also bowing of the bone. He made no mention of neurofibromatosis as being a factor in his cases. Inglis<sup>7</sup> examined the material from Wade's cases and described fibrous and fibroblastic tissue between the ends of the fragments "such as might be found in a simple connective tissue new growth." In his paper he presents photomicrographs of material from 2 of his patients and describes the intimate intermingling of the "connective tissue" with the adjacent osteoid tissue in a manner which from the description seems to be similar to that found in sections from the ununited fracture of the tibia in our case. It would seem possible that the pseudarthrosis reported by him may have been due to the presence of a neurofibroma.

In this connection it should be emphasized that the differentiation of neurofibromatous tissue from fibrous and connective tissue of other origins may be most difficult in many instances. On other occasions the cellular structure and arrangement make the differentiation easier. In our case the similarity of the tissue from the area of pseudarthrosis to that of the localized tumor of the bone, which was definitely neurofibroma, assisted in the differentiation.

In cases of "congenital pseudarthrosis" search should be made for evidences of neurofibromatosis, including café au lait spots, tumors of peripheral nerves and roentgen evidence of other bony lesions. The absence of manifestations of neurofibromatosis elsewhere does not exclude the possibility of neurofibroma of the bone

4. Brooks, B., and Lehman, E. P.: The Bone Changes in Recklinghausen's Neurofibromatosis, *Surg., Gynec. & Obst.* **38**:587, 1924.

5. Scott, C. R.: Congenital Pseudarthrosis of the Tibia, *Am. J. Roentgenol.* **42**:101, 1939. Kite, J. H.: Congenital Pseudarthrosis of Tibia and Fibula, *South. M. J.* **34**:1021, 1941.

6. Wade, R. B.: So-Called Congenital Pseudarthrosis of the Tibia, *J. Coll. Surgeons, Australasia* **1**:181, 1928.

7. Inglis, K.: The Pathology of Congenital Pseudarthrosis of the Tibia, *J. Coll. Surgeons, Australasia* **1**:194, 1928.

as the etiologic factor in the given case, since neurofibroma of bone has been demonstrated without recognizable lesions elsewhere.<sup>8</sup>

The possibility that the pseudarthrosis may be due to the presence of neurofibromatous tissue should be considered at operation in all instances of "congenital pseudarthrosis." Detailed studies should be made of the tissue removed at the operative procedure to demonstrate or exclude the possibility of neurofibroma, with the realization that superficial examination may suggest the diagnosis of "scar tissue." If neurofibroma is present, incomplete excision of this tissue may lead to recurrence and thus be a factor in the failure of union.

#### SUMMARY

A case which presented bowing of the tibia and the fibula, pathologic fractures and pseudarthrosis associated with neurofibromatosis is reported.

Pathologic examination revealed intraosseous neurofibroma as a factor in the production of the fractures and in the retardation or prevention of union.

In cases of "congenital pseudarthrosis" the patient should be examined for stigmas of neurofibromatosis, which include café au lait spots, extraosseous tumors and roentgen evidence of other skeletal defects. In operations on patients with "congenital pseudarthrosis" the possibility that the process may be due to the presence of neurofibroma in the area should always be considered. If neurofibroma is the cause of the pseudarthrosis, incomplete excision of the tumor with local recurrence may be a factor in nonunion.

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8. Desanto, D. A., and Burgess, E.: Primary and Secondary Neurilemmoma of Bone, *Surg., Gynec. & Obst.* 71:454, 1940.

# PAIN IN THE SHOULDER GIRDLE, ARM AND PRECORDIUM DUE TO FORAMINAL COMPRESSION OF NERVE ROOTS

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In a previous publication<sup>1</sup> attention was directed to a series of cases in which radicular pain radiating to the shoulder girdle, the arm and the precordium originated in the cervical portion of the spinal column and was due to arthritic changes. The symptoms and the diagnosis were discussed, and a suspension type of traction therapy was suggested. It was further suggested that overhead traction was of distinct value as a diagnostic aid. Particular attention was directed to the precordial reference of cervical radicular pain and to the necessity for differentiating this type of pain from true anginal pain.

Since this earlier publication, it has been possible to study a much larger group of cases of the condition described, and an opportunity has presented itself to study and observe many other conditions which simulate this one in the syndrome produced. It was accordingly deemed advisable to supplement the previous publication with an article emphasizing the differential diagnosis and the use of overhead traction as a diagnostic aid.

## PATHOLOGY

It must be stated frankly that the mechanism of the impingement on nerve roots in these cases is still obscure. This is obviously due to the fact that it is not possible to see by direct vision the changes responsible for the impingement. Many interesting suggestions have been offered, as well as some ingenious roentgenologic investigations. The hypotheses can be best understood if one first considers briefly the anatomy of the cervical intervertebral foramen.

The foramen is bounded anteriorly by the posterior surfaces of the vertebral bodies, which are covered by the posterior longitudinal ligament. The upper and lower margins are formed by the concave borders of the pedicles of the superjacent and subjacent vertebrae. The posterior margin is the synovial membrane and ligaments of the apophyseal joint.

It has been suggested by Oppenheimer<sup>2</sup> that the foramen may be narrowed by a breakdown of any of the tissues that normally hold in place the bones that form the foramen. Thinning of an intervertebral disk may represent such a breakdown. Whatever the cause of the thinning of the disk, it is obvious that as the space between the vertebrae diminishes, the height of the foramen diminishes. The forward displacement of the superior articular process of the subjacent vertebra which occurs must of necessity cause a similar decrease in the lateral diameter.

1. Hanflig, S. S.: Pain in the Shoulder Girdle, Arm and Precordium, *J. A. M. A.* **106**:523-526 (Feb. 15) 1936.

2. Oppenheimer, A.: (a) Diseases Affecting the Intervertebral Foramina, *Radiology* **28**:582-592 (May) 1937; (b) Narrowing of the Intervertebral Foramina as a Cause of Pseudorheumatic Pain, *Ann. Surg.* **106**:428-440 (Sept.) 1937.

In the cervical portion of the spinal column degenerative changes in the intervertebral disks occur most frequently from the fifth to the seventh cervical vertebrae. The fact that the nerve roots associated with these vertebrae are larger than the upper cervical nerve roots may explain the frequency of radicular symptoms originating at these levels. It has been thought that spur formations and bridgings are secondary irritative phenomena incident to the narrowing of the disks and the approximation of bony surfaces.

Oppenheimer further suggested that the foramen may be encroached on and narrowed by the formation of bony or inflammatory tissue. Into this group may fall primary apophysial arthritis with resulting thickening of synovial, ligamentous and periosteal structures. This concept may explain the manner in which a single trauma or chronic trauma due to malalignment or postural strain may produce radicular irritation. One must also think of a posterior exostosis occurring in such a location as to encroach on the foramen.

Whichever mechanism is accepted as the one producing the narrowing of the intervertebral foramen, one must conclude that it is but a predisposing factor and that there is an additional inflammatory element superimposed on it. Otherwise, one could not explain the lasting beneficial effects of traction or high voltage roentgen radiation.<sup>3</sup> One cannot expect traction or roentgen therapy to restore the thickness of a thinned intervertebral disk or to reduce the size of an exostosis. I take exception to a statement by Oppenheimer<sup>2b</sup> that "the considerable narrowing of the foramen thus caused is quite sufficient to account for marked compression of nerve roots," and that "it is unnecessary to assume, under these conditions, some additional inflammatory reaction of soft tissues—which, by the way, has never been observed at operation or autopsy." There must be an added inflammatory factor. Traction affords relief by temporarily increasing the size of the foramen and allowing the neuritis caused by friction to subside. Similarly, high voltage roentgen radiation reduces the edema and congestion of inflammatory tissue and by doing so probably increases the foraminal space.

#### CLINICAL PICTURE OF IMPINGEMENT ON A NERVE ROOT

Whether the cause of impingement on a nerve root is the increase in size of an exostosis, the narrowing of the foramen due to inflammatory encroachment or the thinning of an intervertebral disk, the clinical picture is always characteristic.

The symptoms are much more frequently referable to the lower cervical than to the upper cervical region of the spinal column. If the irritation is in the latter region, the pain begins in the upper posterior region of the neck and radiates up over the occiput toward the temporo-frontal region. This pain is commonly referred to by the patient as a headache and is usually worse in the morning. It may be associated with a burning or an aching sensation in the occiput.

If the symptoms arise in the lower cervical region, the pain is referred to the top and back of the shoulder and the outer border of the arm. From there it may travel into the outer aspect of the forearm, the wrist or the fingers. There may be paresthesias of any of the fingers of the hand. Commonly, however, these are confined to the thumb and index fingers. The pain is often referred to the precordium and may simulate and be mistaken for anginal pain.

The type of symptoms produced is further influenced by the amount of impingement and the portion of the nerve root involved. Any portion of the nerve root, sensory, motor or even sympathetic, may be involved. Sensory are more frequent

3. Kelly, LeM. C.: Chronic Hypertrophic Osteoarthritis in the Cervical Spine with Radiculitis. *New York State J. Med.* 42:336-340 (Feb. 15) 1942.

than motor changes. This may be due to the fact that the motor fibers of the anterior cervical roots are fewer than the posterior sensory fibers, comprising a bundle only one-third the size of the latter. The degree of impingement may cause variation in sensory changes, from paresthesias and numbness to severe intractable pain. Similarly, if the motor fibers are involved, there may be reflex changes, loss of strength, atrophy and even flaccidity.

If the pain is well established, it is usually influenced by one or more motions of the neck. It has been suggested that the cervical foramina narrow in flexion and open in extension. If this were so, one would expect that such pain would be routinely made worse by flexion in all cases. This, however, is not so. In many patients the pain is acutely accentuated by extension; in others, it is made worse by flexion, and in still others it is influenced by rotation.

The pain is increased by anything that tends to elevate the pressure within the spinal meninges, such as coughing, sneezing and defecation. If very severe, it may even be influenced by deep breathing and laughing. If the condition has progressed for some time, the pain may become unbearable. The patient usually carries the head stiffly and resists whichever cervical motion accentuates the pain. The pain is usually worse when the patient is in the recumbent position. It is not uncommonly so severe that ordinary doses of narcotics are of little help.

#### DIAGNOSIS

If the symptoms that present themselves approximate those described in the foregoing section, it is important to make a thorough differential study, eliminating other disorders that can produce similar symptoms. This can be done by taking the history carefully, making complete orthopedic and neurologic examinations, including roentgen studies with particular attention being paid to special views, and noting the response of the patient to overhead suspension traction (fig. 1).

*Roentgen Studies.*—The roentgen projections should include: first, an antero-posterior view of the cervical part of the spinal column sufficiently large to include the cervical ribs if they are present; second, a lateral view carefully taken so that it visualizes clearly the lower cervical vertebrae; third, an oblique view of each side of the cervical part of the spinal column. The securing of correct oblique views has been difficult. To secure satisfactory views one must use meticulous roentgen technic. The technic has been carefully outlined by Fuchs.<sup>4</sup> Certain important changes must be noted. Narrowing of the intervertebral disks is significant (fig. 2A). Exostoses must be sought for, particularly at the posterior borders of the vertebral bodies (fig. 2B). Narrowing of the intervertebral foramen must be noted, particularly when associated with narrowing of a disk. It is best seen in the oblique view (fig. 2C). Protrusion of exostoses into the foramen may be visualized both in the lateral and in the oblique views. The absence of any visible changes does not preclude the possibility of impingement on a nerve root. The impingement may be due to capsular and ligamentous thickening, which of course does not reveal itself by roentgenogram. Roentgenograms are usually taken in a single plane, and significant changes which are not seen in that particular plane may be overlooked. It has been demonstrated that hypertrophic changes may be extensive and roentgen evidence of the changes absent.<sup>5</sup>

*Suspension Traction as a Diagnostic Aid.*—The response of the patient to overhead suspension traction (fig. 1) is a diagnostic aid. The apparatus has a striking

4. Fuchs, A. W.: Cervical Vertebrae, Radiog. & Clin. Photog. **16**:34-41, 1940.

5. Parker, H. L., and Adson, A. W.: Compression of Spinal Cord and Its Roots by Hypertrophic Osteoarthritis, Surg., Gynec. & Obst. **41**:1-14 (Jan. 14) 1925.

psychotherapeutic effect. In using the apparatus an attempt has been made to determine that type of response which may be judged to be psychic and to avoid this side effect if possible.

The patient sits in the apparatus as in figure 1, with the heels resting lightly on the ground. Traction is applied until the buttocks swing clear above the seat. The patient has been previously told that when he is suspended his pain may diminish, disappear, increase or remain unchanged. He is asked to note any change while suspended and any further change on being lowered to the sitting position.



Fig. 1.—Patient seated in the portable apparatus for overhead suspension traction.

If the patient has friction neuritis due to narrowing or crowding of the foramen, as suggested in a foregoing section, the response is typical and constant. The patient will state that when he is lifted off the seat the pain diminishes or disappears. He will state further that it returns to its former intensity the moment he is lowered to the sitting position. Any variation of this response must be viewed with suspicion. If the response is atypical, suspension traction should be repeated a day later. Occasionally the correct response is not present at the original stretching but develops at the next stretching. A proper response to stretching assures an early cure by traction in every instance. A delay in the return of pain after the patient is lowered is a side effect which has been found to be psychic. This delay may vary from a few minutes to several hours or even a day.



## DIFFERENTIAL DIAGNOSIS

Impingement on a nerve root of the type under discussion must be differentiated from other conditions which can produce the same symptoms.

*Disorders of the Shoulder Joint.*—Impingement on a cervical nerve root must first be differentiated from various injuries and diseases of the shoulder joint.

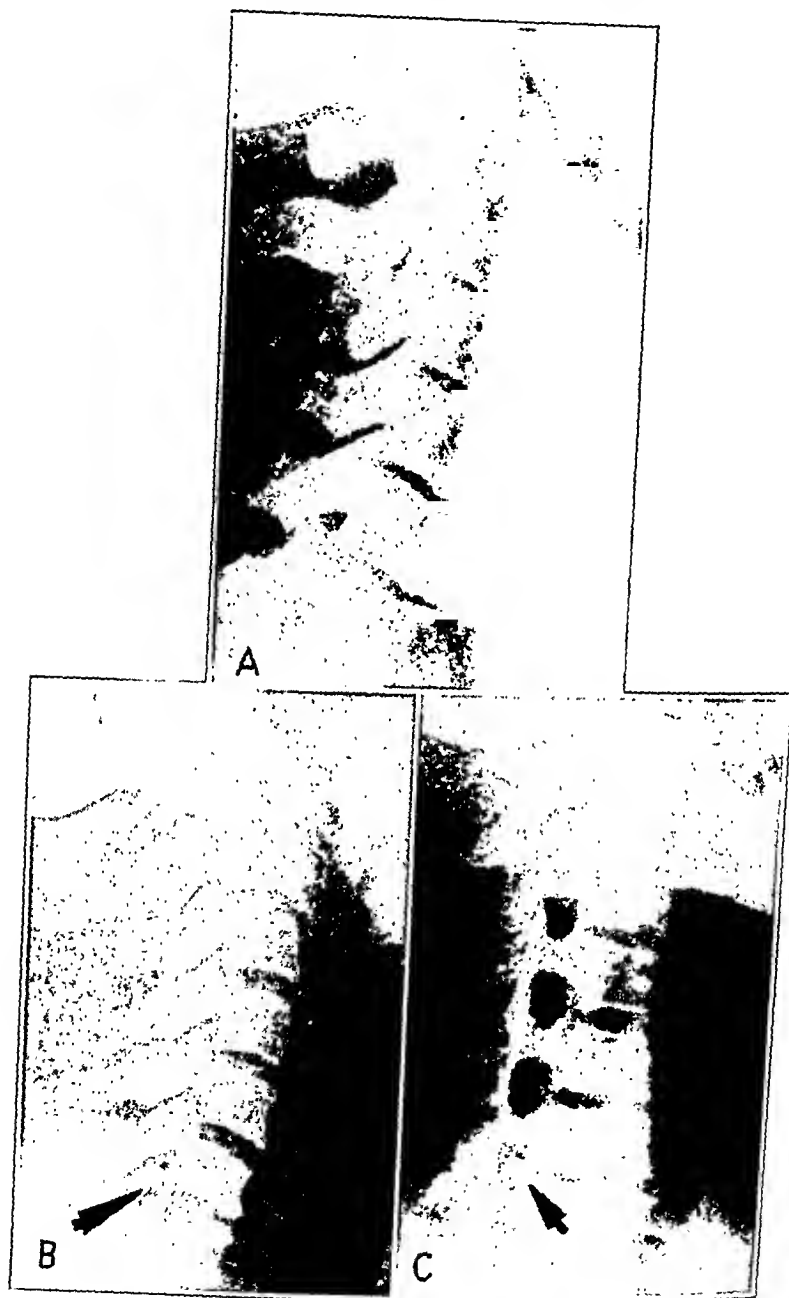


Fig. 2.—*A*, narrowing of the intervertebral disks with compensatory spur formation. *B*, posterior exostosis of the sixth cervical vertebra. *C*, oblique view demonstrating a narrowed intervertebral foramen.

A careful history noting the relation of the pain to motions of the shoulder and leading questions as to whether it is difficult or painful to remove the clothes or comb the hair will usually suffice. Examination of the shoulder in a search

for sensitive points, restriction of motion and accentuation of pain on motion will further establish whether the shoulder joint or any of its allied structures is the source of the pain.

*Cervical Rib Syndrome.*—The average patient with a cervical rib syndrome is younger than the patient who has impingement on a nerve root. It is rare to see impingement on a nerve root due to foraminal compression much before the age of 35 to 40. The pain of a cervical rib is usually not felt in the neck but is more commonly felt only in the forearm and hand. The paresthesias in the hand are more likely to be confined to an ulnar distribution. They may, however, have a radial distribution. Here too the pain may be influenced by rotation and extension of the neck. It may be made worse by a downward tug of the arm and shoulder. There are frequently vasomotor symptoms, which may vary from dusky discoloration to diminution or obliteration of pulses. Coughing and sneezing may accentuate the pain, probably by jarring the irritated and sensitive structures at the site of the cervical rib. The patient may hold the head stiffly and may dislike moving it. Frequently, holding up the affected arm passively with the other arm will relieve the pain. The response to overhead suspension is exactly what one would expect and is of diagnostic value. Pulling up the head produces the same effect as pulling down the arm and shoulder. Accordingly, the pain is made worse with suspension traction, and the patient states that the pain decreases when he is lowered. The diagnosis is further simplified by roentgen disclosure of cervical ribs. Therefore, although the history and the description of symptoms may not make it possible to differentiate adequately a cervical rib syndrome from the syndrome of impingement on a cervical nerve root, roentgen studies and suspension traction do.

The cervical rib syndrome has been relieved almost consistently by the wearing of an airplane splint. Shrugging exercises designed to develop and shorten the trapezius muscle are instituted as soon as the brace is applied. They do much to decrease the postural descent of the shoulder which precipitates symptoms. Thus the exercise does much to prevent a recurrence. It has not been necessary in my experience to resect a cervical rib or to divide a scalenus anticus muscle for the relief of pain. The following report concerns a case in point.

A 27 year old man, married, first presented himself on Aug. 30, 1940, with a chief complaint of pain in the right arm associated with numbness of the right thumb and forefinger. Twelve days previously he noticed pain in the right scapular region. Four days later the pain traveled to the right side of the neck and radiated into the right arm and forearm. At the same time there developed numbness in the right thumb and forefinger. The pain had been made worse by defecation, coughing and motions of the neck, particularly in extension. He had noticed loss of strength of the right hand.

The patient was well developed and well nourished. He held his neck stiffly, with his head inclined forward and to the right. Rotation of the cervical part of the spinal column to the left or hyperextension of this part of the spinal column accentuated the pain. The right shoulder was normal. The radial pulses were equal. Overhead suspension increased the pain strikingly. The pain returned to its previous state when the patient was lowered.

A roentgen examination made on August 30 was reported as follows: "There is a cervical rib on each side. The supernumerary ribs are unusually long, particularly that on the left side."

The patient was put into an airplane splint, and his condition responded promptly. The acute symptoms subsided in one week, and the residual symptoms disappeared in one month.

Comment: To be noted are the aggravation of the patient's pain by coughing and defecation, motions of the neck and suspension traction.

*Scalenus Anticus Syndrome.*—This syndrome is not as common as one would expect from the extensive literature on the subject. In my experience the diagnosis has been made rarely, and when it was made there was some doubt as

to the existence of such a clinical entity. When the syndrome is judged to be present, the observer notes that the symptoms are essentially those seen with the cervical rib syndrome. It responds to the use of an airplane splint and to the exercises already described. Overhead traction accentuates the pain.

It has been possible occasionally to cure the condition by intermittent suspension traction in spite of the early accentuation of pain. This may be due to eventual stretching of the scalenus anticus muscle and release from its constricting effect. As for any tenderness over the scalenus muscle, so often described, it has been found to be of no help as it is a fairly constant normal finding. Nachlas<sup>6</sup> in a recent publication disputed the occurrence of a scalenus anticus syndrome and suggested that cutting of the scalenus anticus muscle allows easier extension of the cervical part of the spinal column and that this in turn opens the intervertebral foramen and relieves pressure on the nerve root. I am not prepared to agree completely with him in regard to this conclusion, but the anatomic considerations and reasoning expressed in the publication are interesting and highly suggestive.

*Ruptured Intervertebral Disk.*—The symptoms of foraminal compression must of course be similar to those produced by herniation of a cervical intervertebral disk. It was possible to stretch a patient with this lesion in the suspension apparatus. There was considerable speculation as to whether marked traction such as this apparatus affords could relieve the symptom momentarily or perhaps allow the disk to shift position so that it might no longer produce symptoms. There was no relief when the patient was suspended, and the response was not typical. Traction of this sort was continued for several days without any particular relief. There was a rather unusual psychic reaction to the traction. The night following the first period of traction the patient slept well for the first time in several weeks. Subsequently the involved region was explored for a ruptured intervertebral disk, and one was removed, with complete cure of the symptoms. Another case may be cited in illustration of this condition.

A 45 year old man was first admitted to the neurosurgical service of Dr. William Jason Mixer, in Boston, because of a pain in the left side of the neck and in the left costocoracoid area, radiating into the left arm, forearm and left second and third fingers, with hyperesthesia and paresthesias of these two fingers. This pain had been present for eight weeks. The patient stated that it was made worse by coughing, sneezing and defecation. There was no injury preceding its onset.

The patient held his head rigidly in the forward and flexed position. All motions of the neck were restricted. Extension of the cervical part of the spinal column increased the pain. The motions of the shoulder joint were normal and did not influence the pain. Neurologic examination revealed nothing but hyperesthesia to pinprick and hypesthesia to brush and vibration in the second and third fingers.

Spinal fluid obtained by lumbar puncture revealed a total protein content of 93 mg. per hundred cubic centimeters. A tentative diagnosis of possible rupture of an intervertebral disk was made, and the patient was discharged to his home on September 21. Directly after this discharge he was seen in my office.

His response to overhead traction was atypical; i. e., the pain was not relieved. Traction was continued for four days and then discontinued. On October 8 the patient was readmitted to the hospital, to the service of Dr. William Jason Mixer. Roentgen studies with iodized poppyseed oil were carried out, and an extramedullary lesion between the sixth and seventh cervical vertebrae was disclosed. On October 13 laminectomy was done and a disk protruding between the sixth and seventh cervical vertebrae, on the left side, was removed, with complete cure of symptoms.

Comment: The physical findings and the history are identical with what one might expect with impingement on a nerve root. The suspension traction response is atypical.

6. Nachlas, I. W.: Scalenus Anticus Syndrome or Cervical Foraminal Compression, *South. M. J.* 35:663-666 (July) 1942.

*Neurofibroma of a Cervical Nerve Root.*—The symptoms caused by a fibroma of a cervical nerve root may completely simulate those of the condition being discussed, and clinically the two conditions may be indistinguishable, particularly early in their development. As the neurofibroma increases in size, the development of neurologic signs below the level of the lesion is of considerable diagnostic aid. A patient was seen whose symptoms were not unlike those that one expects with impingement on a cervical nerve root. The patient received overhead stretching. The response was atypical. After four days of overhead stretching, lumbar puncture and roentgen studies with iodized oil were carried out and revealed a large filling defect. It is interesting to note that a careful neurologic examination made after the patient was referred for studies by lumbar puncture revealed unmistakable signs below the level of the lesion, suggesting a lesion of the spinal cord. A report of this case follows.

A 47 year old man was seen early in April 1936 because of pain in the right hand and posterior aspect of the right shoulder of two years' duration. The pain was made worse by hyperextension, coughing and defecation.

Examination revealed restriction of extension of the cervical part of the spinal column with accentuation of the pain on forcing extension. The motions of the shoulder joint were normal and did not influence the pain. There was slight atrophy of the muscles of the right arm and shoulder girdle and some weakness of the right hand grip. Response to overhead traction was atypical.

Traction was continued for four days without relief. The patient was then referred to the neurosurgical service of Dr. William Jason Mixter. A careful neurologic examination revealed Hoffmann's sign on the right side and absence of the abdominal and cremasteric reflexes on the right side. Spinal fluid obtained by lumbar puncture revealed a total protein content of 220 mg. per hundred cubic centimeters. Roentgen studies with iodized oil revealed a filling defect on the left side, and on June 25 a large neurofibroma was removed, with cure of the symptoms.

*Paralysis of the Serratus Anterior Muscle.*—Paralysis of the serratus anterior muscle when due to trauma may produce pain in the neck radiating to the upper scapular region and to the arm. The pain may be referred from there into the hand and may be associated with paresthesias of the fingers. It is not influenced by motion of the shoulder joint. It may be accentuated by hyperextension of the neck. It is not influenced by coughing, sneezing or defecation. The patient's response to stretching of the neck is atypical.

This condition may result from anything which produces a sudden downward thrust of the shoulder. I have observed it following the carrying of heavy logs on the shoulder. In another instance it was observed following the carrying of hods of coal by a patient who was physically unused to such activity. It was seen again following an effort to replace on an overhead shelf a large mixing bowl that threatened to fall, by an upward thrust of the palm and outstretched arm. The condition is easy to diagnose if one remembers to ask the patient to reach forward with the affected arm. If the shoulders are viewed from behind, there is characteristic winging of the scapula (fig. 3). The condition usually responds to the carrying of the arm in the airplane position. Recovery is usually complete. The following report illustrates the differential diagnosis.

A 51 year old man was first seen on Nov. 15, 1941 because of a pain in the left side of the neck radiating into the left arm and forearm and associated with numbness of the finger tips of the left hand. Two weeks previously he had carried some heavy logs on the left shoulder. The pain was not made worse by coughing, sneezing or defecation. The patient was referred for treatment with a diagnosis of cervical radiculitis.

Examination of the patient's left shoulder gave negative results. Hyperextension of the cervical part of the spinal column accentuated the pain. There was no relief of the pain with overhead suspension. The neurologic examination gave negative results. When the patient

reached forward with the left arm held horizontally at the level of the shoulder, there was extraordinary winging of the scapula.

The patient carried his arm in an airplane splint. The pain declined rapidly, and the winging disappeared in two months.

*Postural Cervical Strain.*—Forward carrying of the head may produce a strain of the cervical spinal muscles with pain in the back of either side of the neck or in both sides of the neck, radiating into one or both arms. There is no accentuation of the pain with coughing or sneezing. The pain is obviously not due to irritation of a nerve root. There may be some discomfiture with certain motions of the neck, due to the tight and shortened structures which are incident to poor



Fig. 3.—Winging of the scapula due to paralysis of the serratus anterior muscle.

posture. It is easy to recognize these cases. Traction has been of some value in stretching shortened structures, particularly if accompanied by postural training.

*Angina.*—The reference of pain to the precordium with impingement on a cervical nerve root has been responsible for a not uncommon mistaken diagnosis of disease of a coronary artery. The reference of pain to the precordium has been explained by Nachlas,<sup>7</sup> who stated that the medial anterior thoracic nerves originate in the eighth cervical and first thoracic spinal segments while the lateral anterior thoracic nerve originates in the sixth and seventh cervical segments and that these nerves and their branches are motor nerves (i. e., they contain no sensory fibers) but that they "can possess protopathic sensations" so that an

7. Nachlas, I. W.: Pseudo-Angina Pectoris Originating in the Cervical Spine, *J. A. M. A.* 103:323-325 (Aug. 4) 1934.

irritation of them may produce a diffuse yet definite pain referred to the terminal portion of the nerve. The absence of a history of pain on exertion and the presence of pain with motions of the neck tend to rule out disease of a coronary artery. Similarly is this true of the continuation of pain for days without constitutional symptoms or other cardiac signs. The relief of pain with suspension traction is a diagnostic aid. The thoracic pain of angina when referred into the arm is more likely to be referred along the inner aspect of the arm, whereas radicular pain is more commonly referred from the cervical part of the spinal column along the outer border of the arm. The differential diagnosis, however, may at times be somewhat difficult. Electrocardiographic studies are of value.

*Hypertrophic Arthritis.*—Osteoarthritis of the cervical part of the spinal column may in and of itself, without impingement on a nerve root, be responsible for a variety of cervical symptoms. These are usually pain and stiffness of the posterior part of the neck, particularly on arising in the morning. The pain may be referred to the occiput, the back of the shoulders or even into the arms. The reference of pain is not due to irritation of nerve roots but probably occurs in the same manner that osteoarthritis of the hip causes pain to be referred anteriorly along the thigh to the knee. The pain is not made worse by coughing or sneezing. There is no release of symptoms with overhead suspension traction.

Too often the presence of pain and stiffness of the neck associated with roentgen findings of osteoarthritis leads to a diagnosis of compression of nerve roots when none exists.

These patients are helped by overhead traction but fundamentally in the same manner that traction helps any osteoarthritic lesion.

*Neurosis.*—If one has the opportunity to see large numbers of patients with symptoms referable to the neck, it becomes apparent that the neck is often selected as a site for neurotic symptoms. A tight, drawing sensation in the back of the neck or a conviction that something is out of place is not an uncommon manifestation of emotional exhaustion and maladjustment. The psychic value of overhead traction in this type of patient is marked, if one wishes to use it with positiveness and assurance. It is equally as effective as the supposed manipulative reduction of a supposedly displaced vertebra. The author has experimentally stretched some of these patients with good results.

#### TREATMENT

Once traction has been decided on as necessary in the light of the history, the results of physical examination and roentgen studies and the response to overhead suspension traction, one has a choice of two types. The suspension type of traction can be continued or it can be replaced by traction in bed. I have preferred to use repeated overhead stretching. The apparatus used for it is a collapsible portable tripod (fig. 1). It can be used in the home, the office or a hospital. A simple but substantial overhead hook or beam to which a set of pulleys and ropes can be secured is equally effective. The traction is usually carried out by the physician. Once intelligent patients have become familiar with the technic, they can carry out the treatment at home. Traction will relieve patients of most of their pain in four to seven days, after which there is gradual disappearance of the residual pain through a period of a week to ten days. The patient is lifted for a moment or two and then lowered. This is repeated for about two to three minutes. This constitutes one treatment period. The suspension treatment is followed by an application of heat and massage to the neck

muscles. The average case calls for three stretching periods on each of the first two days, two on each of the next two days, and then they are spaced out as needed. A Thomas collar has been used occasionally.

This type of traction has three advantages: It permits the patient to be ambulatory; it does not require admission to a hospital. When effective, it is rapid.

For patients who have become difficult to handle because of long-standing pain and for others who prefer bed and hospital care, traction in bed is a good substitute. This type of traction can be carried out effectively in a cardiac bed by using its tilting mechanism as suggested by Dr. Armin Klein (fig. 4). The same effect may be secured by elevating the head of the conventional bed on blocks or on a chair. Traction is maintained by the use of 5 pounds (2.3 Kg.) on each arm of the Sayre sling, or by a 10 pound (4.5 Kg.) total weight if one uses a

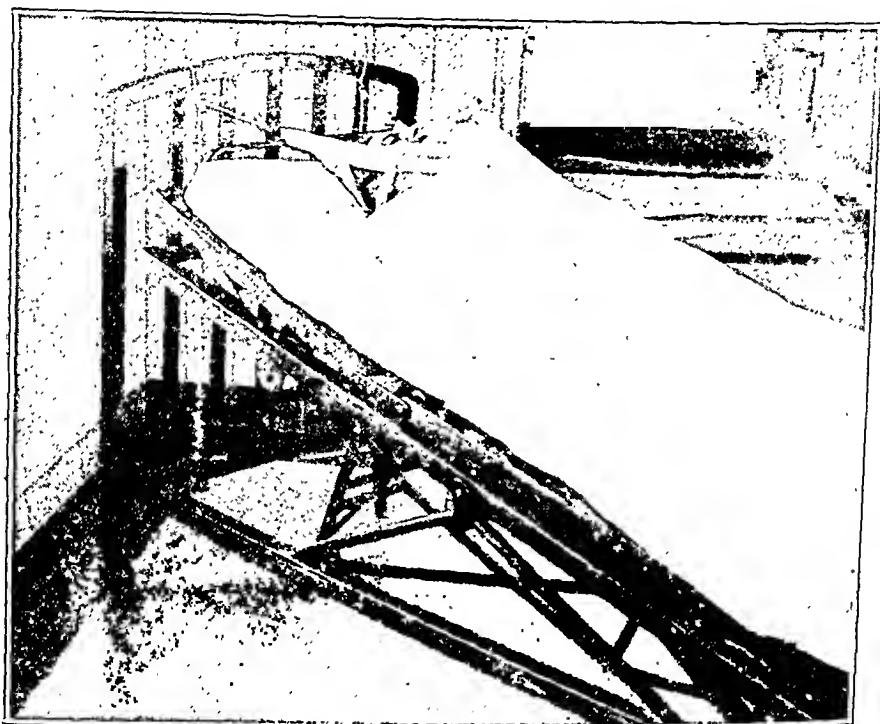


Fig. 4.—Continuous traction applied by the use of the cardiac bed.

crossbar to allow the patient to turn from side to side while maintaining traction. Traction is continued for two hours, after which the patient is allowed a rest of twenty minutes. This procedure is carried out alternately throughout the day. If the patient can sleep in the apparatus, he is encouraged to do that.

Recovery with this type of traction is slower than with the overhead type. Many patients find it extremely difficult to stay under continuous traction in bed, because they are uncomfortable.

As to the possibility of danger incident to overhead traction, one can state that it is a technic that can be utilized without fear. It is perfectly safe and may even be carried out by the patient's family after they have been instructed in its proper use. The period of elevation must be short, the ropes used must be of good quality, and if an overhead hook or beam is used as a point from which to hang the apparatus, it must be secure. If the patient has false dental plates, it is wise to have him bite on a flat sterile sponge during elevation.

## SUMMARY

Pain in the shoulder girdle, the arm or the precordium may be due to foraminal compression of a cervical nerve root. The diagnosis is suggested by pain uninfluenced by motion of the shoulder and definitely related to motion of the neck. The pain is usually made worse by anything that increases intrameningeal pressure, such as coughing, sneezing and defecation. The condition responds to overhead suspension traction or to traction in bed. The technic of suspension traction is described, and its use as a diagnostic aid is emphasized.

The condition must be differentiated from many other disorders which can produce similar symptoms. The differential diagnosis is not difficult. A careful taking of the history is necessary. The examination must be complete and must include a thorough neurologic study. The response to suspension traction is a distinct diagnostic aid.

371 Commonwealth Avenue.



# THE CENTRAL BONE GRAFT IN JOINT ARTHRODESIS

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SPRINGFIELD, MASS.

About two years ago there was presented before the American Academy of Orthopedic Surgeons a brief communication on the technic of using a central bone graft in arthrodesis of the knee or the ankle.<sup>1</sup> The procedure was developed at the Springfield Unit of the Shriners' Hospital for Crippled Children in 1929, and at the time of reporting 10 patients so treated had been followed through their period of growth and the relative leg lengths were compared with those in a like series in which arthrodesis had been achieved by other methods, chiefly the Hibbs method.

## Summary of Data on Forty-Four of a Total of Sixty-Seven Patients Treated by Arthrodesis of the Knee or the Ankle

Knee						Ankle						
Patient	Age at Operation, Yr.	Shortening, Inches		Follow-Up, Yr.	Diagnosis	Patient	Age at Operation, Yr.	Shortening, Inches		Follow-Up, Yr.	Diagnosis	
		Pre-operative	Post-operative					Pre-operative	Post-operative			
D. B.	5	1½	¼	4	Tuberculosis	L. D.	10	¾	2½	4	Poliomyelitis	
R. B.	8	½	¼	5	Tuberculosis	M. B.	12	1¼	¾	4	Poliomyelitis	
J. D.	14	2	2	2	Poliomyelitis	J. D.	13	¾	0	2	Tuberculosis	
W. B.	10	¾	0	4	Tuberculosis	H. B.	13	2	2	2	Poliomyelitis	
C. K.	9	¾	0	4	Tuberculosis	S. P.	15	1¾	¾	1	Poliomyelitis	
A. N.	13	¾	0	3	Sepsis, old	P. P.	12	2	2	2	Poliomyelitis	
J. A.	10	0	¼	4	Tuberculosis	B. M.	13	2	2½	2	Poliomyelitis	
E. Mac.	6	0	½	5	Tuberculosis	P. H.	11	¾	1¼	4	Poliomyelitis	
C. St. L.	11	0	0	3	Sepsis, old	A. F.	14	2½	1¾	2	Poliomyelitis	
R. H.	4	0	0	4	Tuberculosis	J. D.	13	1½	¾	3	Spina bifida	
R. R.	12	½	¾	2	Tuberculosis	B. K.	12	¾	½	2	Poliomyelitis	
Average		0.5	0.2			F. B.	14	1½	1¼	3	Poliomyelitis	
Previously reported cases of arthrodesis of knee, 10; total 21						J. O.	15	2	2	1	Poliomyelitis	
						S. B.	14	4	4	3	Poliomyelitis	
						R. N.	9	0	0	4	Poliomyelitis	
						N. P.	13	2¼	2	2	Poliomyelitis	
						R. O.	12	1	1	2	Poliomyelitis	
						D. M.	16	2	1½	1	Poliomyelitis	
						R. McD.	12	½	0	2	Poliomyelitis	
						J. McN.	12	1½	1½	2	Poliomyelitis	
						J. O.	14	1¾	1½	2	Poliomyelitis	
						D. B.	12	1¾	2	2	Poliomyelitis	
						P. B.	12	2	1	2	Poliomyelitis	
						Average		1.6	1.3			
						Total number of cases of arthrodesis of ankle						23
						Grand total.....						67
												44
With insufficient data because too recent.....						23						

The average age at operation was approximately 9 years, and the resulting inequality of leg length in both groups amounted to about 1 inch (2.5 cm.). Therefore, it appeared evident that a bone graft crossing the central part of the epiphyseal disks did not arrest growth.

At the time of reporting these cases I was not able to offer a scientific explanation in support of the indisputable clinical evidence that interference with growth did not result from the procedure. Naturally this led to considerable doubt, and to be doubted by one's friends is distressing, if not entirely damning. It was therefore extremely gratifying when Aries<sup>2</sup> showed experimentally that the longitudinal growth of bone does not take place in the form of lines parallel to the epiphyseal

1. Hatt, R. N.: J. Bone & Joint Surg. 22:393 (April) 1940.

2. Aries, L. J.: Surg., Gynec. & Obst. 72:679 (April) 1941.

disk but by successive cones from the endosteal surface, each new cone having for its base the peripheral portion of the disk and possessing a wider perimeter than the old.

Sixty-seven operations of the type previously described have been recorded at the Shriners' Hospital, and of these 44 are sufficiently complete as regards pre-operative and postoperative measurements and follow-up to permit further evaluation of the method. The accompanying table is more or less self explanatory.

It will be noted that the average age of patients treated by arthrodesis of the ankle is considerably higher than that of patients treated by arthrodesis of the knee. The indication for operation in the former group was talipes calcaneus with an associated quadriceps weakness, the stabilization of the ankle and the foot permitting one to discard supportive apparatus. The number of cases selected for the operation indicates the regard for its usefulness at the Springfield unit of the Shriners' Hospital for Crippled Children.

#### SUMMARY

Further evidence is offered that a centrally placed graft does not cause arrestment of growth. The usefulness of the procedure justifies the opinions previously stated.

146 Chestnut Street.

## HENRY JACOB BIGELOW, ORTHOPEDIC SURGEON

GEORGE H. JACKSON JR., M.D.  
EVANSTON, ILL.

Monday, the second day of November 1846, dawned cold and cloudy in Boston and the cheerless sky was leaden throughout the day. Darkness was upon the town before half after five and the cold wind began to blow from the bay, with the evening flow of the tide. Few people walked about the quiet streets, and the clatter of an occasional carriage seemed to intensify the unpleasantness of the weather by raising dismal echoes ordinarily muffled in the bustle of the busy thoroughfares.

In Summer Street, the cheery glow of parlor lights meant that most of the good dwellers in that fine neighborhood were staying indoors for the evening, but at no. 27, Dr. Henry Jacob Bigelow bundled into his great coat and ventured forth to make a call. He walked up to Washington Street, where a north turn and a few more steps brought him to Bromfield Street, turned into Province Court and finally reached Montgomery Place, where he stopped before no. 8 and knocked. While waiting to be admitted, he noted the neat lettering on the doorplate—"Dr. O. W. Holmes"—and felt the pocket of his coat to assure himself that he still had with him the fold of papers he had taken from home.

Dr. Holmes came to the door, greeted the visitor cordially and led him to the library where the Autocrat's comical smile and friendly manner seemed the more pleasant because of the bright glow which came from the fireplace and danced over the red carpet and made grotesque shadows behind the statues of the "Fighting Gladiator" and the "Dying Warrior" on top of the bookcases which lined the room. Titian's portrait of Vesalius looked down from the wall, and Rembrandt's "Three Trees" was obscured in the shadow at a distance from the fireplace. Bigelow laid the fold of papers on the green-covered drum table, and host and guest settled into great armchairs to enjoy the warmth of the fire.

All about the room were books, some of which had belonged to Holmes's father, author of the highly regarded "Annals of America," and there were copies of Holmes's "Poems" and of his "Old Ironsides," once printed as a handbill by a Boston newspaper and so widely circulated that an aroused public sentiment saved the historic ship from proposed abandonment and dismantling. A copy of "The Contagiousness of Puerperal Fever" was there too, still unaccepted and refuted by leading obstetricians three years after its publication. Most of the books in the library dealt with anatomy, and the great folios with their fine plates and stout bindings were the very ones which Harvard medical students may see today if they visit the library in the anatomy building.

Books were familiar friends to Bigelow too, and his father was also a writer, whose essay "On Self-limited Diseases" and handsomely illustrated "American Medical Botany" had been classic contributions to a growing American scientific literature. The younger Bigelow had been awarded the Boylston Prize two years before for his "Manual of Orthopaedic Surgery," and the purpose of the visit to Holmes this evening was to seek the opinion of a valued friend on the merits of another article that had been prepared in the short space of two weeks.

The friendship between Holmes and Bigelow began shortly before 1838, was firmly established during the year Bigelow spent in Hanover, N. H., while attending the course of lectures on anatomy which Holmes gave at Dartmouth Medical School, and endured for well over half a century. There was much in common

between the two men; each was the son of a well known writer and himself an author, both had attended Harvard Medical School and had enjoyed the benefits of postgraduate work on the continent of Europe, at the completion of which they had returned to Boston to assume teaching positions of importance in their alma mater and staff appointments of responsibility at the Massachusetts General Hospital. A further bond was the cordial relationship between Holmes's and Bigelow's father, who had collaborated in 1839 to bring out a revised American edition of Marshall Hall's "Principles of the Theory and Practice of Medicine." It was natural then, when he had prepared the account of a matter he believed of utmost importance, that Bigelow should seek the advice and encouragement of his dear friend the professor.

As the two sat facing each other in the library, Bigelow recounted the story of the great discovery disclosed at the Massachusetts General Hospital on the 16th of October past. He had been present in the surgical amphitheater when Dr. John Collins Warren had allowed Dr. Morton to give the first public demonstration of a new method of producing artificial anesthesia by inhalation, and it had been a complete success. Pain during operations could be abolished and the surgeon would be permitted to operate more deliberately and in regions of the body heretofore inaccessible to the scalpel. Neither the full significance nor the vast potentialities of this new gift to surgery were overlooked by Bigelow, and he had become an enthusiastic devotee of the inhalation of ether and had demonstrated the safety of the procedure by frequently administering the vapor himself. He told Holmes that on the following day he would read the paper he had prepared at the monthly meeting of the American Academy of Arts and Sciences, and apparently received the unreserved endorsement of his friend, for on November 3 was presented to the world the first public announcement of America's greatest contribution to medicine, emancipation from the physical and mental torture which for centuries had been the inevitable concomitant of all but the simplest of surgical procedures.

No printing of Bigelow's paper was ever issued by the American Academy of Arts and Sciences, but in 1852, under the heading "Two Hundred and Seventy Eighth Meeting, November 3, 1846," the following brief note is given: "Dr. Henry J. Bigelow gave some account of a new process of inhalation employed by Dr. Morton, of Boston, to produce insensibility to pain during the performance of operations by the dentist and the surgeon."<sup>1</sup> Had the academy printed the whole address shortly after its delivery by Bigelow, the bibliography of this important writing would have been made a very simple matter. However, the first printing of "Insensibility During Surgical Operations Produced by Inhalation" appeared in the issue of the *Boston Medical and Surgical Journal* for Nov. 18, 1846; so the conscientious bibliophile will want both the academy's notation of the speech and the number of the aforementioned journal for November 18. Probably because of the great demand for copies of this number of the journal, it was reissued later in the year. This item is rarely encountered and is easily mistaken for the original issue. A fourth item plagues the avid collector, the separately issued reprint of Bigelow's paper, an eight page pamphlet without a wrapper, existence of which was unknown until a few years ago, when a number of copies were uncovered in Boston.

Bigelow contributed several important works on anesthetics, among them an analysis of the relative merits and dangers of ether and chloroform, which appeared

1. Proceedings of the American Academy of Arts and Sciences, Boston, Metcalf & Co., 1852, vol. 1, p. 38.

in 1848, and an accurate historical review of the development of inhalation anesthesia in 1876. The first student's textbook to contain a chapter devoted to the use of ether was R. U. Piper's, "Operative Surgery, Illustrated," printed in Boston in 1852.<sup>2</sup> The author dedicated the book to Bigelow, acknowledged his indebtedness to both Holmes and Bigelow for the use of books from their libraries in preparation of the volume and reprinted in its entirety the latter's "Anaesthetic Agents," which had been prepared at the request of the Surgical Committee of the American Medical Association. In this paper Bigelow prophesied that the duty of administering ether "will soon be recognized as involving an entirely distinct responsibility from that of the surgeon who performs the operation." To Bigelow must also be accorded the honor of having transmitted the first communication of the new ether discovery to reach Europe in his letter to Dr. Francis Boott, of London.

Well known as are his writings on anesthesia, Bigelow gave to American medical literature several classic contributions in other fields, particularly on surgical repair of bones and the removal of stones in the bladder. His intense interest in surgical problems dated from his early manhood, and it is related that when Dr. James Jackson tried to persuade the young man to follow his best advantage and choose a medical career in the footsteps of his father, the reply was, "I'll be damned if I won't be a surgeon."

The medical student of a century ago followed the apprentice system then in vogue, whereby he studied under the private supervision of a preceptor for a period of three years, during which he attended two or three courses of lectures at some recognized medical school before taking a final examination for the degree. Pursuant to this custom, Bigelow began his medical education in the office of his father, continued study in Paris, France, for several years and returned to America to take his degree at Harvard University in 1841. Intensive application and close observation had made Bigelow highly competent in the then new arts of auscultation and percussion, and his equal as a microscopist was not to be found in all New England. At the time of his appointment as surgeon at the Massachusetts General Hospital he had become recognized as a most careful, deliberate and competent surgeon, whose ingenuity in devising improved operative technics and in designing or modifying existing surgical instruments and appliances seemed limitless. It is recorded by Dr. H. H. A. Beech that at one time there was hardly an instrument in the cases of the operating room of the Massachusetts General Hospital which had not been designed by the masterful chief of service or which did not show some new advantage from Bigelow's having worked with it. Among such improvement were tourniquets for the arm, wrist and thigh, needle holders, handles for drills, retractors for use in amputation, arterial forceps with a device for disengaging ligatures, an operating chair, an apparatus for angular extension and a most complete autopsy table.

Although the bibliography of Bigelow's papers lists some three score items, they are confined chiefly to the fields of anesthesia, litholapaxy and orthopedic surgery, and it is on the last group that present interest is centered. In 1844 the Boylston Prize was won by Bigelow's "Manual of Orthopaedic Surgery," written in answer to the assigned question, "In what cases, and to what extent, is the division of muscles, tendons, or other parts, proper for the relief of deformity or lameness?" This book was a tall octavo, bound in either red or black cloth, and of about 200 pages. It covered a scope far wider than the prize question designated, and was a most carefully written composition, the first comprehensive

2. Piper, R. U.: *Operative Surgery Illustrated*, Boston, Ticknor, Reed & Fields, 1852.

presentation of the subject of orthopedics in the United States. Much of the material of the book dealt with subjects not now considered within the province of orthopedic care, such as the chapters on strabismus and stammering, though the former was the most complete discussion that had yet been printed in America, and the latter gave full evidence of the author's thorough understanding of the complicated mechanism involved in the mechanics of speech. Bigelow's discussion of tenotomy, torticollis, clubfoot, spinal curvature, contractions of the hand and fingers, and the appendix, with its instructions on the use of plaster for making casts, is now of only antiquarian interest, since it is no longer the custom to divide the genioglossus muscle to aid an unfortunate stammerer or to cut the lateral ligaments of the knee joints of rachitic children with knock knee. The manual is, however, still a work of historical value for the comprehensiveness of its presentation of the many operations in use at the time of its publication and furnishes a noteworthy picture of the best contemporary French surgery. One statement in regard to the treatment of clubfoot Bigelow caused to be printed in italics: "When in distortion of long standing, with a certain degree of motion still remaining in the joint, a tendon evidently hinders the limb from assuming a normal position, it should be divided."

The first attempt at resection of the head of the femur to be made in this country was reported by Bigelow in 1852. The patient was a young boy with what was apparently tuberculosis of the hip joint complicated by a large abscess and posterior dislocation of the femur. In the belief that removal of the upper end of the dislocated bone would hasten repair of the abscess present, a preoperative decision was made to attempt a hitherto untried method of treatment. Although the patient failed to return to health after operation, great credit must be given the surgeon for his courageous pioneer attempt in a field of surgery previously unexplored.

At the January meeting of the Boston Society for Medical Improvement in 1858, Bigelow exhibited a specimen of stellate crack of the radius removed from a patient who had died as a result of extensive injuries. The correct diagnosis of this type of fracture had been made by comparison with the clinical picture of a similar injury he had observed two years previously. Attention was called to the fact that such an injury of bone involved no displacement of the fragments and that the resultant swelling of the joint and limitation of motion were apt to be mistakenly regarded as the sequels of nothing more serious than a simple sprain of the wrist. Little may be added to Bigelow's explanation of the manner in which such fractures are incurred. He declared that in certain instances of trauma the bones of the wrist acted as a wedge to spread the corresponding hollow of the radial extremity, producing the stellate type of splitting fracture.

As a result of training in the use of the microscope, pathologic processes were interpreted by Bigelow in terms of the cellular pathology of Virchow rather than those of the older gross pathology generally accepted in his day. An instance of his practical application of the newer science is shown in a paper on the periosteal reproduction of the condyles of the humerus, published in 1867, in which is described the excision of the ends of all three bones entering into the formation of the elbow joint in a patient with an infection involving the synovial membrane. The specimen removed after subsequent amputation of the arm showed to Bigelow's satisfaction that the muscle groups at the lower end of the resected humerus were attached to newly formed, curved, cone-shaped condyles resulting from regeneration of periosteal tissue left in position at the time of operation. Further evidence of the application of surgical pathology and the physiology of tissue repair is contained in Bigelow's publication, in 1868, of a report on the handling of

ununited fractures. He described 11 ununited fractures of long bones in all of which he had determined before operation to attempt to obtain solid union by virtue of the osteoblastic properties of the periosteum. How well he performed the technical details involved in the operations is proved by the fact that in 10 of the fractures healing went on to solid union, the single failure being one in which definite infection was present before the surgical intervention. The principles underlying the surgical technic as defined in this report correspond closely with those of the present day, and the warning against unwarranted stripping of the periosteum beyond actual needs is still heeded. Bigelow's particular method of using wires for fixation during the period of bone regeneration, though not now followed, was adequate to provide the immobilization necessary for successful union.

It may still be customary for students reviewing the surgical treatment of fractures to generalize by saying that all injuries to the elbow except fractures of the olecranon are treated by rest in flexion at a right angle. This aphorism harks back to Dr. Bigelow's discussion of methods of treatment of fractures and dislocations of the elbow joint in the *Boston Medical and Surgical Journal* in 1868. The ancestors of the student's general rule is found in the summary of this excellent treatise in the author's words:

. . . Ascertain if the olecranon is broken, which can be done with comparative ease, as it lies near the surface; this injury requires special treatment. In all other injuries of the elbow joint, whether you are able to make an exact diagnosis or wholly unable to do so on account of the swelling, treat them as though the forearm had been dislocated backwards, and secure the arm at about right angles to an inside angular splint.

A final word of caution is given against overenthusiastic attempts at passive motion in recently injured joints, because of ensuing pain and reaction in muscles if such attempts are carried too far. Bigelow considered a slow restoration of function by gradual use of the injured member on the part of the patient a far better method of therapy.

Best known of Bigelow's orthopedic works is "The Mechanism of Dislocation and Fracture of the Hip," issued in 1869, an epitomization of three papers presented at various times before the Boston Society for Medical Improvement, the Massachusetts Medical Society and the American Medical Association, conveying the results of researches which had extended over a period of eight years. Previous to the appearance of this classic demonstration of a new method of reduction, most hip dislocations had been treated by extremes of traction in the hope that stretching of the muscles would permit the return of the dislodged femoral head, but Bigelow proved by painstaking study of dissections that the anterior portion of the capsule of the hip joint was of very great strength and density and that its two divergent bands, simulating a letter Y, were the chief obstacle to the successful reduction of dislocations. It was shown conclusively in this communication that if the capsular ligaments remained intact in whole or in part after injury they determined the general clinical picture encountered in such cases of trauma and that the muscular resistance to replacement of the femur was of only secondary importance. Reduction by the method devised by Bigelow depended on relaxation of the tensed Y ligament by flexion of the thigh on the pelvis and subsequent traction or rotation of the flexed femur to replace it in the acetabulum, under which conditions of manipulation the strong capsular structures were a help rather than a hindrance to reduction. At the conclusion of the portion discussing dislocations, the book contains a section devoted to the diagnosis and treatment of various types of fracture of the neck of the femur and some notes on pelvic fractures.

In a day when roentgenography was not at hand to render immediate and exact portrayal of the situation and the character of bone injuries, there was much discussion among surgeons of the difficulties of determining whether a fracture of the neck of the femur was of the intracapsular or the extracapsular type. In a communication in 1875, Bigelow felt obliged to go on record with the dictum that such discussions rendered patients no service and that it was far more important in all instances of injury to a hip to decide whether an impaction of the bone was present or not. Studies of numerous sectioned femurs had convinced him that the architecture of the lamellar structure at the junction of the neck and the shaft proved that the former was simply a continuation of the latter, somewhat flattened in order to bear weight more efficiently. He considered that fractures of the neck were of two types, impacted fractures of the base, and unimpacted fractures of the rest of the neck, without regard for the capsule, and that treatment for both types was the same.

In addition to papers already mentioned, Bigelow wrote several short notices on various phases of his work with fractures and in 1878 brought forth the classic exposition of his method of breaking up stone in the bladder and removing the fragments by flushing. Few indeed have won the distinction of contributing accounts of fundamental achievement in as varied fields of medical science as did Bigelow. His works on anesthetics, fractures, and dislocations of the hip and in the province of urology will endure as long as an American medical literature exists.

Paying tribute to his former chief, a Boston physician once wrote that no one who had spent a year at the Massachusetts General Hospital under Dr. Bigelow "could fail to recognize the effect on his own subsequent career of the time thus spent. The subtle influence over his students was felt the more for being insensibly exerted." All who have been privileged to serve under Dr. Osgood know how truly this expression of regard applies to their own former chief, whose kind sympathy and ready understanding will never be forgotten.

*His ready smile a parent's warmth exprest,  
Their welfare pleas'd him, and their cares distrest.*

Some of Dr. Osgood's house pupils of a score of years ago recall the thrill of the visit of the honored guests who came in the uniforms of the British Army to pay their respects to Colonel Brackett and Dr. Osgood, who had lately set aside his own uniform. It was a great privilege to see in familiar wards Sir Anthony Bowlby, the renowned British surgeon general, consulting surgeon to the British Expeditionary Forces, tall, erect, taciturn and bronzed with years in the South African service, and to walk far to the left of the genial Welchman, Sir Robert Jones, whose merry smile and ready wit charmed all. They were amazed at the apparently limitless flow of statistics of casualties in the British Army that Sir Anthony quoted from a little black book no larger than a playing card, which he carried in a pocket of his blouse.

A large group made rounds on that well remembered morning. The visitors were met under the rotunda by Drs. Washburn, Brackett and Osgood, together with all members of the orthopedic service, and, with due observance of the proprieties of military rank, proceeded to ward I. An incident of the visit is well recalled by some of the interns present. As the inspection of the ward progressed to the men's side of the ward, there was an obvious stir among the patients as the round came abreast of the bed of a Canadian ex-soldier, bedfast with a badly infected tuberculous knee. The soldier seemed rather frightened at the sight of the British uniforms and in evident confusion raised a trembling, thin, white hand and began



muttering something not heard by any of the group of doctors. With characteristic intuition and keen sympathy for the feelings of others, Dr. Osgood cast a questioning glance in the direction of his senior houseman, and, sensing that the Canadian patient was upset, quietly turned the attention of his followers to the bed beyond, leaving Sir Anthony by the bedside of the soldier to speak a few quiet words. It was not until the next day that the senior intern learned from the soldier the cause of his emotional disturbance. The poor fellow had been helpless to overcome the humiliation of being bedridden and unable to stand at attention properly to deliver the salute due the wearer of the Cross of the Royal Victorian Order; "but the General had shaken his hand, and actually talked with him, and he knew the 'Old Man' under whom he had seen service, and had wished him speedy recovery."

No doubt Henry Jacob Bigelow, the first orthopedic surgeon at the Massachusetts General Hospital, looked down on the gathering of orthopedic surgeons of a later generation and showered his blessing on Sir Anthony Alfred Bowlby, Sir Robert Jones and Robert Bayley Osgood.

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#### IMPORTANT WORKS OF HENRY JACOB BIGELOW

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# ARTHROGRYPOSIS MULTIPLIX CONGENITA

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"Arthrogryposis (or arthrogryphosis) multiplex congenita" is a term used to designate contractures of the joints. The term "arthrogryposis" is a combination of two Greek words, meaning literally a crooked or bent joint. Various writers have described this condition under different names, such as "multiple congenital contractures of joints," "amyoplasia congenita," "myodystrophia congenita" and "myodystrophia foetalis deformans."

In 1841 A. G. Otto described a case of congenital myodystrophy and in 1905 E. Rosenkranz collected 56 cases which were similar in nature and labeled them arthrogryposis multiplex congenita. Stern<sup>1</sup> in 1923 and Lewin<sup>2</sup> in 1925 used this term in reporting their cases. W. Sheldon<sup>3</sup> in 1932 preferred the name "amyoplasia congenita," believing that the initial lesion is primary aplasia or hypoplasia of certain muscle groups, the defects of the joints being secondary. He confirmed his ideas by investigating the electrical reactions of the affected muscles; these showed no reaction of degeneration but the faradic responses were weak or absent; there were no sensory or trophic changes. D. S. Middleton<sup>4</sup> in 1934 used the term "myodystrophia foetalis deformans," believing that the deformities result from fatty degeneration of muscles occurring during intrauterine life. He expressed the belief that the muscular degeneration is analogous to the muscular dystrophies of later life. The microscopic appearances are very similar. He stated that the muscular degeneration arises fairly late in intrauterine life, after the muscle fibers have been fully differentiated, and that the condition progresses rapidly during late fetal life and ceases at birth.

Arthrogryposis is not mentioned in textbooks of orthopedics except in the recent texts of Campbell<sup>5</sup> and Steindler.<sup>6</sup> These authors have described the congenital contractures of the joints and have recommended early corrective measures.

## OBSERVATIONS IN EIGHTEEN CASES

During the years 1925 to 1942, 18 patients (10 males and 8 females) were admitted to the Children's Hospital in Boston with the diagnosis of arthrogryposis. The ages ranged from 5 days to 10 years and 7 months. There is no history of deformity in relatives or parents in 17 of the cases. In 1 case the maternal uncle, aged 20 years, has never walked.

The following tabulation summarizes the combinations of abnormalities of the joints in these patients.

Patients	Areas Involved
2	Hands and feet
1	Hands, feet and hips
2	Hands, feet, knees and hips

1. Stern, W. G.: Arthrogryposis Multiplex Congenita, J. A. M. A. 81:1507 (Nov. 3) 1923.
2. Lewin, P.: J. Bone & Joint Surg. 7:630, 1925.
3. Sheldon, W.: Arch. Dis. Childhood 7:117, 1932.
4. Middleton, D. S.: Edinburgh M. J. 41:423, 1934.
5. Campbell, W. C.: Operative Orthopedics, St. Louis, C. V. Mosby Company, 1939.
6. Steindler, A.: Orthopedic Operations, Springfield, Ill., Charles C Thomas, Publisher, 1940.

Patients	Areas Involved
1	Hands, elbows, feet and knees
1	Feet, knees and right hip, which is dislocated
1	Hands, feet, elbows, knees, hips
1	Hands, feet and hips, which are both dislocated
1	Feet and right hip, which is dislocated
2	Feet, knees, hips and spine
1	Feet, knees, hands and hips, both of which are dislocated
2	Feet, hands, elbows and hips, which are both dislocated
1	Feet, hands, knees, hips and spine
1	Feet, hands, knees, shoulders
1	Feet, hips and spine

In addition to contracture of the hip, 5 patients had frank dislocation of the hip, bilateral in 3, unilateral in 2. Several of the children presented additional anomalies. There were 2 with undescended testicles, 3 with inguinal hernia and 1 with a cleft palate.

On examination in cases of arthrogryposis the extremities present a unique appearance. They lack the usual anatomic contours, having instead a stuffed sausage-like appearance. Very little muscle is palpable. The structures overlying the joints feel thickened and contracted. Dimples are frequently seen over the patellas and the elbows. In most of the involved muscles passive correction of the contractures is possible to a few degrees, although some are rigid, allowing no correction. These gross abnormalities are symmetric, distinctive and readily recognizable.

Histologically there is atrophy and fat replacement of the involved muscles.

Roentgen films taken in the first few months of life show deficient muscle shadows, with increased density in the capsular areas, without changes in the bone. Older infants and children show secondary deformities of bones associated with long-standing contractures of the soft tissues.

In general, the younger patients in this series were treated in this order: (1) manipulations without anesthesia, (2) supports, (3) anesthesia, manipulations and supports and (4) surgical corrections.

The older patients were treated by operative procedures selected as most suitable for the correction of the individual deformity. These procedures were fasciotomy, capsulotomy, lengthening of tendons, open reduction of hips and arthrodesis for the correction of club feet.

The end results varied in relation to the number of deformities present and the time of treatment. As is true of all congenital deformities, the best results were obtained with the early institution of corrective measures. These badly disabled children, presenting at birth a discouraging picture, were definitely improved by treatment.

#### REPORT OF AN ILLUSTRATIVE CASE

The case record of a patient illustrating the progress made from the age of 3 weeks to that of 26 months follows:

R. S., a boy aged 3 weeks, was admitted to the outpatient department of the Children's Hospital in Boston, Aug. 29, 1940, for the treatment of deformed upper and lower extremities, noted at birth. The father, aged 32 years, had diabetes. The mother, aged 22 years, was well except for occasional attacks of dermatographia. The patient was the only child; there had been no other pregnancies. The parents reported no deformities in their families.

At the birth of the child the mother had twilight sleep and was "on the delivery table for twenty-four hours." No instruments were used at delivery, although there was some type of

manual manipulation to improve the position. Episiotomy was done. No cyanosis or convulsions followed birth.

The infant since birth had been fed by formula. There was considerable difficulty in feeding him, due to vomiting. Vitamins C and D were given at 3 weeks of age.

Immediately after birth it was noted that the baby had deformities of the shoulders, elbows and hands, contracted knees and clubfeet.

On examination, both shoulders were adducted with passive abduction to 90 degrees. The deltoid muscles were small, with very little muscle that was palpable. The elbows were extended to the extreme degree and permitted passive flexion of 45 degrees on the right and

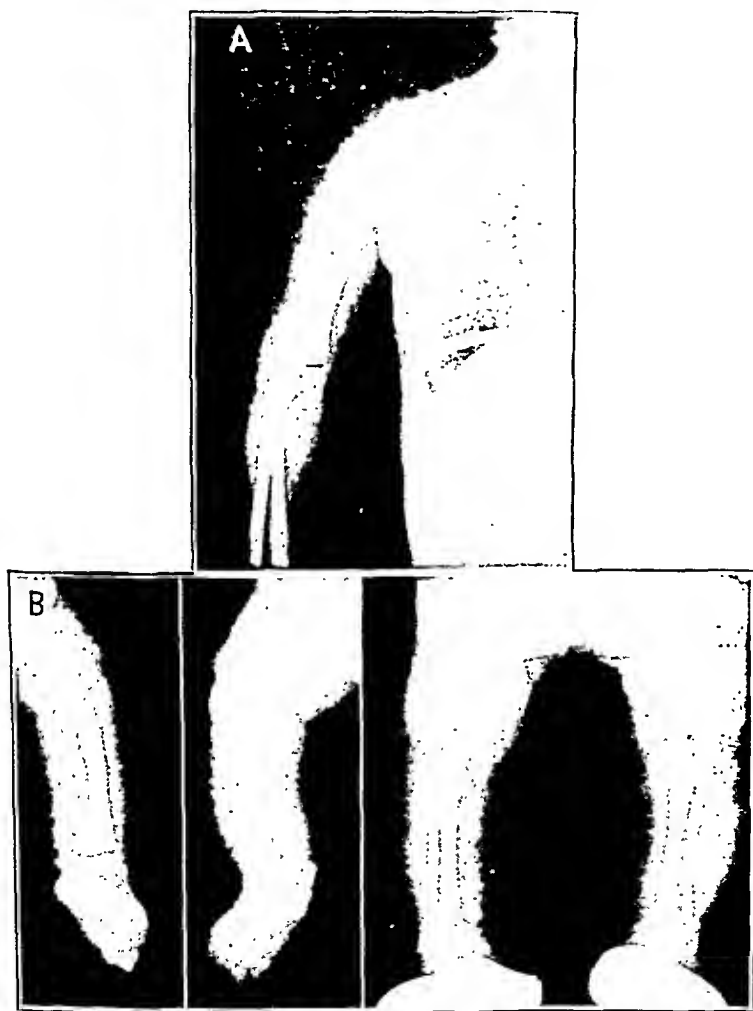


Fig. 1.—*A*, roentgenogram showing poorly developed muscles of the upper arm. *B*, roentgenograms showing diminished muscle shadows and thickened periarticular structures.

80 degrees on the left. Supination of the forearm was not possible on the left; 15 degrees was obtainable on the right. Pronation of the forearm on the left was 20 degrees, that on the right was 15 degrees. Extension of the wrist on the left was 20 degrees; that on the right, 20 degrees. Flexion of both wrists was possible to 50 degrees. Knees were permanently flexed to 25 degrees, with further flexion to 120 degrees. Both feet were in rigid equinovarus position.

Roentgenograms of the upper and lower extremities showed deficiency of the muscle tissue shadows. The capsules and the ligaments appeared thickened. The bones were normal except for the deformities in the clubfeet.

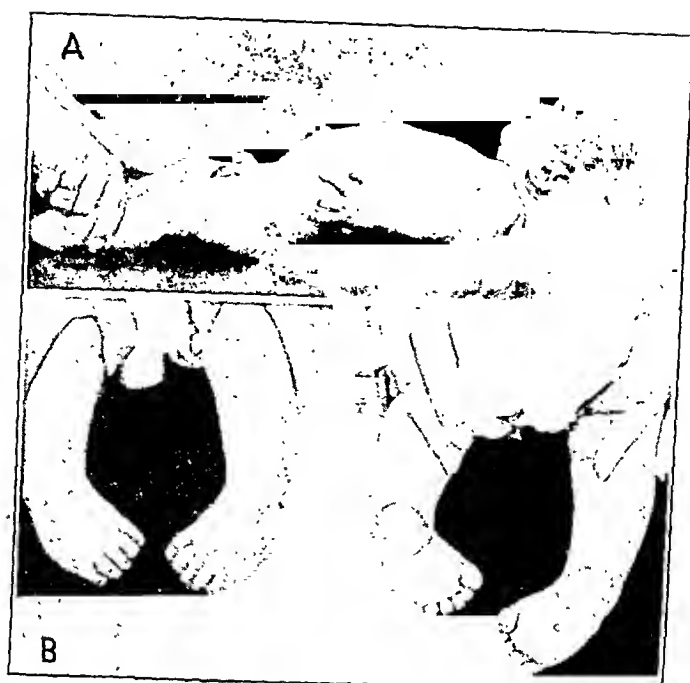


Fig. 2.—*A*, patient at 3 weeks. Note contractures of the feet, knees, fingers and elbows. *B*, rigid talipes equinovarus.



Fig. 3.—*A*, patient at the age of 10 months, prior to surgical correction of the feet, *B*, lower legs of the patient twelve weeks after operation—aged 12 months and 2 weeks.

The child was given outpatient care, consisting of manipulations of the upper and lower extremities with weekly changes of casts to the feet, for a period of ten months. During this time he had recurrent infections of the upper respiratory tract with otitis media.

The infant at 10 months of age was admitted to the hospital for surgical correction of his feet and further manipulation of his upper extremities. Lengthening of both heel cords and posterior capsulotomy were done, and casts were applied with the feet in marked dorsiflexion, abduction and eversion. Following an uneventful convalescence of three weeks, the boy was again followed in the outpatient department. There physical therapy was given to the upper extremities three times weekly. His feet were protected in casts for eight weeks, followed by manipulations three times weekly. Bivalved casts were used between treatments. At 16 months of age he began to walk in corrective shoes. His feet were manipulated daily at home, and Dennis-Brown shoe splints were used during his day and night sleeping periods.

At the time of writing the patient is 2 years and 3 months of age and is attending a nursery school. Although he has not a complete range of motion of his elbows and shoulders,

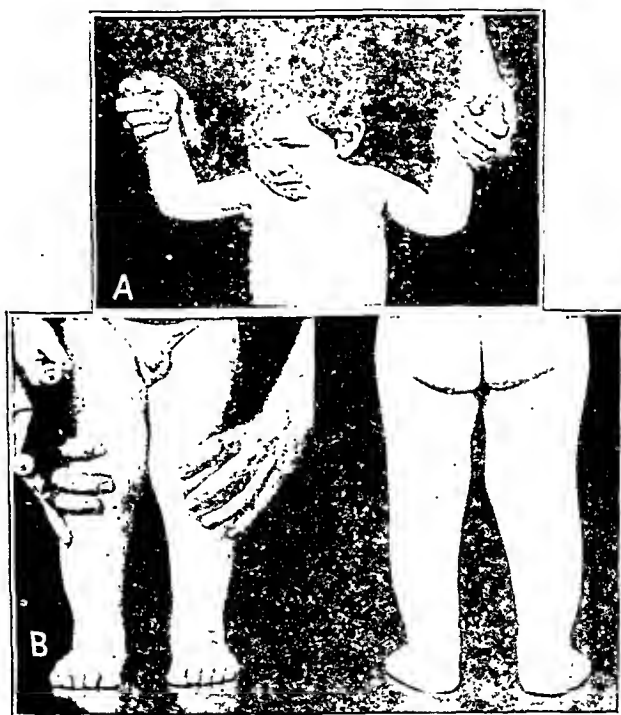


Fig. 4.—A, patient at the age of 26 months, showing corrected elbows. B, corrected feet and knees.

he uses his hands and arms freely in performing the various nursery activities. He is talking well for a child of his age.

His last examination, in November 1942, showed a good hand grasp, with some weakness; there were no contractures of fingers or wrists; the elbows had active flexion of 90 degrees and extension of 160 degrees; shoulder abduction was, active, 60 degrees; passive, 90 degrees. Both feet were flexible and corrected 10 degrees beyond neutral in dorsiflexion, abduction and eversion. He walked and ran well and easily. His arms swung freely but not completely.

Besides the orthopedic treatment, this patient has been given an abundance of vitamins, including vitamin E. He has been receiving vitamin E since June 1941, when he was 10 months of age, and is now having 15 drops daily of a preparation of this vitamin.

270 Commonwealth Avenue.

7. The preparation used is tocopherex (Squibb), a concentrated distillate of vegetable oils each cubic centimeter of which represents 400 mg. of mixed alpha, beta and gamma tocopherols, equivalent in vitamin E activity to 250 mg. of alpha tocopherol.

## WIRE FIXATION OF FRACTURES OF THE PROXIMAL THIRD OF THE HUMERUS

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A relatively high percentage of fractures of the proximal third of the humerus in which the fragments are completely displaced are difficult or impossible to reduce satisfactorily by manipulation. This is especially true of the fracture-dislocations and of those fractures in which the head of the humerus is also broken into two or more pieces. These fractures are likewise difficult to treat by traction, because the short proximal fragment tends to be abducted and rotated outward while the pectoralis major and subscapularis muscles tend to draw the proximal end of the distal fragment inward and forward. When traction is applied in abduction, the proximal end of the distal fragment is drawn forward and downward by the pectoralis major and latissimus dorsi muscles (fig. 1 *A*).

On account of the difficulties mentioned, it is my custom to treat these fractures by open reduction, frequently without even attempting treatment by closed manipulation or traction. This is particularly true since I have learned to place a powdered sulfonamide compound in the wound and thus lower the chance of infection almost to the vanishing point.

The operative reduction is relatively simple and may be done with the patient under general or local anesthesia. The technic is as follows:

The patient is placed on his back on an ordinary operating table and is so draped that the fractured extremity can be manipulated without the operative field becoming contaminated. The fractured arm lies at the side with the elbow resting on a sand bag and the forearm resting on the chest.

A vertical incision about 3 inches (7.5 cm.) long is made on the anterolateral aspect of the shoulder. The incision begins just below the margin of the acromion and is parallel with the fibers of the deltoid muscle. The fibers of this muscle are separated by blunt or sharp dissection, care being taken not to injure the circumflex nerve, which lies on the deep surface of the muscle near the middle of the incision and frequently at the level of the fracture.

The muscle is retracted gently, leaving the nerve stretched across the wound. The distal end of the proximal fragment lies just beneath the deltoid muscle and is easily identified. The proximal end of the distal fragment lies some distance inward and forward and can be felt with the finger. The clot is removed, an assistant makes moderate traction on the arm with the elbow flexed, and the surgeon reaches in with a large Kocher forceps or a small bone-holding forceps, grasps the shaft of the humerus near the fracture line, pulls it directly outward and opposes its end to that of the proximal fragment.

If the fragments are quite stable when reduced (fig. 2 *A*), no internal fixation is necessary. The powdered sulfonamide compound is implanted in the wound, the wound is closed in layers and the arm is immobilized across the chest with a Velpeau bandage. As a rule, only one small blood vessel is tied. This is the vein lying alongside the circumflex nerve. If it is torn, care must be taken not to damage the nerve in clamping and tying the vein.

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From the Department of Surgery of the Washington University School of Medicine.

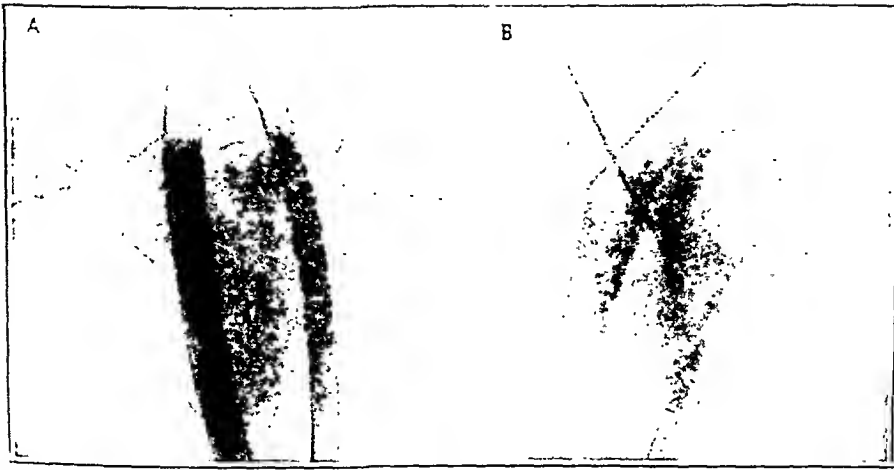


Fig. 1.—*A*, fracture of the proximal third of the humerus. The roentgenogram shows the position obtained by traction in a Thomas arm splint. *B*, the same fracture as in *A* after open reduction and immobilization by two Kirschner wires, which were removed later. The fracture of the head of the bone is not visible in the roentgenogram.

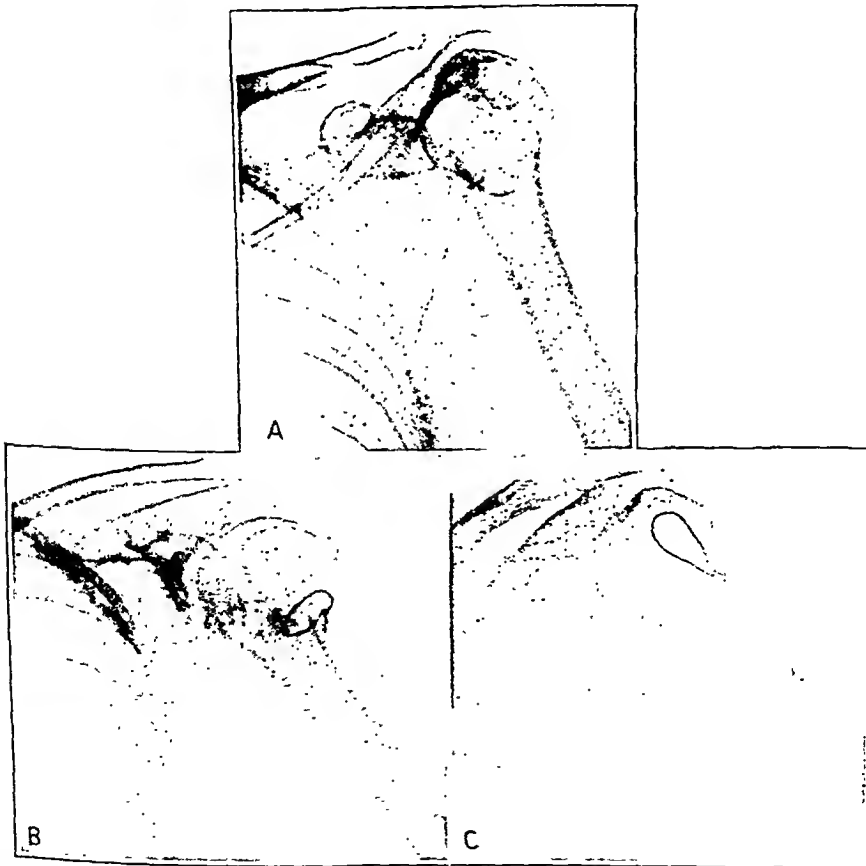


Fig. 2.—*A*, fracture similar to that in figure 1 after open reduction. The fragments were stable when reduced, and no internal fixation was necessary. *B*, a similar fracture fixed by a single wire loop. *C*, a similar fracture fixed by a wire mattress suture.



Ten days after the operation the Velpeau bandage is removed, the cutaneous sutures are taken out and a hanging cast is applied to the extremity with the elbow flexed 90 degrees. The cast extends from the upper arm to the wrist and is suspended at the wrist by a bandage which passes around the neck. The patient is then instructed to exercise the shoulder muscles several times daily by bending forward and swinging the arm backward and forward and across the body and in circles while the wrist is supported by the sling from the neck. About three or four weeks later, the cast is removed, and the exercises are continued until the shoulder is normal.

In most instances it will be found that the fragments are not stable when reduced and that some form of internal fixation is advisable. I have generally used a small loop of stainless steel wire, either a double or a single loop (fig. 2 *B* and *C*). The double loop is more secure, and the twist in the wire is placed farther away from the floor of the subdeltoid bursa and thus is less apt to cause pain afterward. However, the double loop is more difficult to apply, and its use prolongs the operation. As most of the fractures of the proximal third of the humerus occur in older persons, this is not desirable. Moreover, if the ends of the fragments are comminuted (and they often are), one may not find suitable spots for the four drill holes necessary for the double loop or mattress wire suture.

In a recent case in which the head of the humerus was split and the greater tuberosity comminuted, it was found that two Kirschner wires drilled through the proximal fragment and obliquely through the cortex of the distal fragment not only fixed the fragments of the head but also afforded adequate fixation of the two major fragments (fig. 1 *B*). With the fracture reduced, suitable points on the lateral and superior aspects of the shoulder are selected and the Kirschner wires are pushed through the skin down to the bone and then drilled through the two fragments. They are then cut off, leaving about an inch (2.5 cm.) of each wire protruding from the skin, and the wound is closed and the arm is immobilized in a Velpeau bandage. The protruding ends of the wires are covered with a gauze pad, and ten days after the operation the cutaneous sutures are removed, the hanging cast is applied and the swinging exercises are started. If the wires are so placed that the exercises are painful, the latter are postponed until the wires have been removed. At the end of two or three weeks, depending on the stability of the fragments, the wires are pulled out and the exercises are continued as described in a foregoing paragraph.

The use of Kirschner wires is the simplest and most satisfactory method which I have found for fixing fractures of the proximal third of the humerus, and they eliminate the necessity of leaving a foreign body in an area where pain is especially prone to occur. As the wires are directed backward and downward there is little danger that their protruding ends will damage an important blood vessel or a nerve.

# TREATMENT IN CASES OF SLIPPED CAPITAL FEMORAL EPIPHYSIS AT THE MASSACHUSETTS GENERAL HOSPITAL

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A study of the records of patients treated at the Massachusetts General Hospital for epiphysiolysis or for slipped upper capital femoral epiphysis was made in an attempt to determine what has been accomplished in treating these patients, what progress has been made in methods of treatment and what procedures should continue to be used and what procedures should be discarded. We surveyed all records filed at this hospital in cases of slipped femoral epiphysis, since the condition was recognized here. We found that various forms of treatment had been used, and we expect that analyses of the results will afford indexes to the proper treatment in such cases.

J. Albert Key<sup>1</sup> and Philip D. Wilson<sup>2</sup> in previously published monographs, reviewed the cases of slipped upper femoral epiphysis as recorded in this hospital from 1904 to 1923. They reported that in 30 cases treatment was by manipulation and plaster fixation or by open reduction and plaster fixation. Key concluded that "forcible manipulation of an old case tends to result in increased stiffening of the hip and is not justified by the results obtained." Wilson disclosed that in the majority of cases the findings at the time of open operation indicated that manipulation could not have succeeded if it had been tried. He therefore advocated open reduction at the seat of the deformity and postoperative fixation with plaster.

The end results obtained during this period apparently were not satisfactory enough to warrant continued reliance on these methods of treatment. A survey of the records of 39 patients treated during the years from 1924 to 1932 still revealed some poor results from the old methods of manipulation and plaster fixation or from open reduction and plaster fixation but revealed better results from open reduction, nailing with a three-flanged nail and early mobilization.

In the past decade the treatment for slipped epiphysis has been rather variable but lately has shown some signs of consistency. Thirty-two patients were treated during this period. Seven patients had bilateral slipped epiphysis; therefore, 39 hips were examined and 36 of these were treated in this clinic.<sup>3</sup>

1. Key, J. A.: Epiphyseal Coxa Vara or Displacement of the Capital Epiphysis of the Femur in Adolescence, *J. Bone & Joint Surg.* 8:53-117, 1926.

2. Wilson, P. D.: Displacement of Upper Epiphysis of Femur Treated by Open Reduction. *J. A. M. A.* 83:1749-1756 (Nov. 29) 1924.

3. The statistics on patients with epiphysiolysis treated at the Massachusetts General Hospital in the period from 1933 to 1942 follow.

Number of patients with epiphysiolysis:

32 (In 7 [21%] condition was bilateral; second hip slipped 7 months to 2 years after slipping of first hip)

Sex and ages of patients:

10 (31.2%) females—ages 8 to 14—average age 12 ±

22 (68.8%) males—ages 9 to 16—average age 13 ±

(Footnote continued on next page)

The patients fall into three classifications according to the methods of treatment used: a miscellaneous group, with multiple forms of treatment; a group treated by arthrotomy, reduction and lateral nailing, and a group treated by lateral nailing in situ.

A method of appraising hip function was suggested by the "index of motion" table of Ferguson and Howorth.<sup>4</sup> Briefly, it consists of designating a factor for each motion according to its importance. The amount of demonstrable motion is multiplied by this factor to give a product for that particular motion. The sum of these products represents "the index of hip motion." An example of the use of the index of motion in a specific case follows:

	Motion	Factor	Product
Flexion	145°	0.4	58
Abduction	45°	0.4	18
Adduction	30°	0.2	6
Rotation			
Internal	30°	0.2	6
External	60°	0.1	6
Extension	10°	0.1	1
			<hr/> 95

On this basis the index of hip motion was then computed for the affected hip as compared with the sound hip. Since such an index of motion does not include pain or limp, it is felt that it lacks certain elements which determine true function of a hip. For this reason, we have assigned only one third value to the index of

#### Physical types:

Females—6 obese; 1 tall and thin (types of 3 unknown)

Males—16 obese; 2 tall and thin (types of 4 unknown)

#### Side involved:

Females—5 right; 3 left; 2 bilateral (left hip first in one case; right hip first in other case)

Males—6 right; 12 left; 4 bilateral (2 right hip first; 2 left hip first)

#### Trauma as an etiologic factor in 37 + %:

4 of 10 girls — 40%

8 of 22 boys — 36%

#### Duration of Symptoms:

Females—2 weeks to 1 year—average 3.4 months

Males—1½ weeks to 2 years—average 7 ± months

#### Treatment before entering hospital:

No treatment 21

Rest in bed 5

Treatment of feet 3

Manipulation and cast 2

Traction 1

#### Diagnosis (at this hospital) before roentgen examination:

Correct in 81%

Incorrect—viz., tuberculosis, sepsis and strain—in 19%

#### Degree of slipping:

Minimal (i. e., 1 cm. or less) in 50%; of these 83% were boys and 17% were girls

Marked (i. e., over 1 cm.) in 50%; of these 61% were boys and 39% were girls

4. Ferguson, A. B., and Howorth, M. B.: Slipping of the Upper Femoral Epiphysis: A Study of Seventy Cases, *J. A. M. A.* 97:1867-1872 (Dec. 19) 1931.

motion and an equal value to the element of painlessness and to that of absence of limp, calling the total of these three elements the percentage of true normal function of the hip.

Index of Motion	Painlessness	Absence of Limp	Total Percentage of True Function of Hip
33.3	33.3	33.3	100

The results of the miscellaneous types of treatment are analyzed in table 1. Ten patients were observed for fourteen to one hundred and four months. The first 6 whose cases are charted showed marked slipping; the last 4, minimal slipping.<sup>5</sup>

In the first 3 patients, with osteotomy at a distance from the seat of the deformity, i. e., at the distal portion of the neck or at the subtrochanteric region.

TABLE 1.—Miscellaneous Types of Treatment

Name	Age	Months After Operation	Post-operative Shortening, inches	Treatment	Percentage			Total Percentage of Function
					33.3 Index of Motion	33.3 Pain	33.3 Limp	
C. de J.	14	39	1½	Osteotomy at distal neck with nailing; sepsis; cup arthroplasty	2.0	33.3	33.3	33.3
W. M.	14	14	½	Subtrochanteric osteotomy and Thornton plate	0.0	0.0	0.0	0.0
W. B.	15	25	2¼	Osteotomy at distal part of neck; sepsis; cast	0.0	33.3	0.0	33.3
C. C.	13	104	½	Manipulation and spica	15.0	33.3	33.3	81.6
J. C.	14	26	¼	Open reduction and nailing; acetabuloplasty	12.1	33.3	0.0	45.4
N. B.	14	31	1½	Manipulation, lateral nailing; open reduction and nailing; cup arthroplasty	7.0	22.2	0.0	29.2
Average.....								37.4%
C. McK.	13	38	0	Drilling.....	25.9	33.3	33.3	95.5
A. P.	12	87	½	Open operation and drilling	29.5	25.0	33.3	88.1
A. C.	13	63	0	Traction.....	17.4	33.3	33.3	84.0
C. S.	14	81	5/8	Biopsy.....	16.3	33.3	33.3	82.9
Average.....								87.6%

were the three poorest results seen in the entire series. All 3 patients had a marked limp. One of the 3 had marked pain. Two had no motion in the involved hip, and the third had practically no motion. The total percentage of function for the involved hip ranged from 0 to 35.3 per cent, averaging only 22.8 per cent of normal. To be sure, a group of 3 is a small sample on which to base conclusions, but when the results observed in them are uniformly so poor, it seems as if this type of procedure might be reserved for older neglected deformities. It seems obvious that to restore normal anatomic relationships the attack should be made on the deformity at its site rather than at a more remote point.

The last 4 patients, with minimal slipping, showed good results with drilling or no treatment. The average total percentage of function was 87.6 per cent.

5. A slip of the epiphysis backward and downward from the femoral neck amounting to no more than 1 cm. was considered to be minimal. Any slip greater than 1 cm. was considered marked.

Table 2 presents the data on 11 patients with marked slipping who were treated by arthrotomy and osteotomy through the epiphysial plate and nailing. In each case an attempt was made to replace the head in its anatomic position and to fix it there by inserting a three-flanged nail from the lateral aspect of the femur through the neck and across the epiphysial plate into the head.

Postoperative treatment in most instances consisted of suspension in traction for two to three weeks. The patient was then allowed to be up and about with

TABLE 2.—*Arthrotomy, Reduction and Lateral Nailing*

Patient	Age	Months After Operation	Postoperative Shortening, Inches	Percentage			Total Percentage of Function
				33.3 Index of Motion	33.3 Pain	33.3 Limp	
S. P.....	14	11	0	22.7	30.0	30.0	82.7
L. St. G.....	11	26	$\frac{1}{2}$ (1 cm.)	29.6	30.0	30.0	89.6
A. S.....	12	59	$1\frac{1}{2}$ (3.5 cm.)	15.8	33.3	0.0	49.1
S. B.....	8	63	$2\frac{1}{4}$ (5.5 cm.)	7.0	33.3	0.0	40.3
J. D.....	15	94	$\frac{3}{8}$ (0.95 cm.)	21.1	33.3	33.3	87.7
F. J.....	16	96	$\frac{1}{2}$ (1 cm.)	24.9	33.3	33.3	91.5
C. J.....	12	87	$\frac{3}{8}$ (0.95 cm.)	23.5	33.3	33.3	90.1
J. J.....	16	54	0	15.2	33.3	25.0	73.5
R. L.....	14	50	$\frac{1}{2}$ (1 cm.)	30.5	33.3	33.3	97.1
O. M.....	11	61	$\frac{1}{2}$ (1 cm.)	33.3	33.3	33.3	100
G. O.....	13	77	0	18.5	25.0	0.0	43.5
Average.....		64.3	Under $\frac{5}{8}$ (1.5 cm.)	....	....	....	76.8

TABLE 3.—*Lateral Nailing in Situ*

Patient	Age	Months After Operation	Postoperative Shortening, Inches	Percentage			Total Percentage of Function
				33.3 Index of Motion	33.3 Pain	33.3 Limp	
J. M.....	9	26	0	33.3	33.3	33.3	100
D. McM.....	16	15	$\frac{5}{8}$ (1.5 cm.)	23.7	33.3	33.3	90.3
M. H.....	15	20	0	32.5	33.3	33.3	99.1
R. G.....	13	12	0	33.3	33.3	33.3	100
R. F.....	13 (L)	12	0	31.4	33.3	33.3	97.0
	14 (R)	5	0	24.1	33.3	33.3	90.7
A. W. Jr.....	13	29	0	21.5	33.3	33.3	88.1
O. B.....	10	39	$\frac{3}{8}$ (0.95 cm.)	31.0	33.3	33.3	97.6
M. G.....	12	39	$\frac{3}{4}$ (2 cm.)	32.3	33.3	33.3	98.0
D. R.....	13 (L)	48	$\frac{3}{8}$ (0.95 cm.)	25.3	33.3	33.3	91.9
	15 (R)	30	...	24.0	33.3	33.3	90.6
M. S.....	12	48	$\frac{5}{8}$ (1.5 cm.)	30.5	33.3	33.3	97.1
E. T.....	13 (L)	13	...	26.9	33.3	33.3	93.5
	12 (R)	25	$\frac{3}{4}$ (2 cm.)	26.9	33.3	33.3	93.5
Average.....		25	Less than $\frac{1}{4}$ (0.64 cm.)	....	....	....	94.8

a non-weight-bearing splint and a high sole on the unaffected side. The brace was worn until roentgen examination disclosed obliteration of the epiphysial line and restoration of the epiphysis with bone comparable in vitality to the adjacent bone of the pelvis and the femur. This whole group was followed for an average period of sixty-four and three-tenths months. Their average index of motion was about two thirds of normal. Only 3 of the 11 patients had pain, and this was of minor degree; 5 had no limp, 3 had a bad limp and 3 had only a slight limp. Their average percentage of normal hip function was 76.8 per cent.

The next and final group (table 3) consists of 11 patients, 3 with bilateral involvement. These patients had only minimal slipping of the epiphysis, less than

1 cm. in extent. They were all treated by lateral nailing in situ without arthrotomy. The nail was introduced into the lateral cortex of the subtrochanteric region of the femur and was driven through the neck, across the epiphysal plate and into the head without any attempt at altering the existing relationship of the femoral head and neck. The hip was immobilized postoperatively by Buck's extension apparatus until the sutures were removed. The patient was then allowed to be up and about on crutches or with a brace until motion in the involved hip joint was free and painless. The average period of observation was twenty-five months. The average index of motion was about 84 per cent of normal. Pain and limp were absent in all cases. The average percentage of normal hip function for the entire group was 94.8 per cent.

#### COMMENT

Analysis of the results of treatment in cases of slipped capital femoral epiphysis revealed the ultimate aim to be a fusion of the epiphysis to the neck of the femur in the position in which it was first discovered or in a corrected, anatomic position. To be sure, the accomplishment of this purpose meant cessation of growth in the involved epiphysal region, but it also meant the termination of farther slipping of the epiphysis, and the last consideration is paramount.

Earlier attempts at correction of the deformity by forcible "closed" manipulation and fixation in plaster led to stiffening of the hip. Later attempts at open reposition of the slipped epiphysis and fixation in plaster gave unsatisfactory results, chiefly because of the resulting traumatic arthritis. But the surgeons learned from these later attempts that though roentgenograms may show a marked widening at the epiphysal plate, the epiphysis is quite firmly attached to the neck, and rarely can this relationship be changed by manipulation without osteotomy. Then the addition of the three-flanged nail to the armamentarium of the orthopedic surgeon made it possible for him to replace the epiphysis in its anatomic position, to fix it there with the nail and then to start early mobilization of the hip joint. Plaster casts became unnecessary. Traumatic arthritis became more infrequent and less severe.

Greater experience with such patients sharpened knowledge of the symptoms. This resulted in the early diagnosis, made when the slip was still minimal. In addition, further experience in the follow-up clinic prompted mindfulness of the early signs and symptoms of involvement of the opposite hip, because statistically about 20 per cent of those affected with a slipped upper femoral epiphysis in one hip will, within two years, have bilateral involvement.

We have surveyed the records of 32 patients with slipping of the upper femoral epiphysis in 39 hips who were treated at the Massachusetts General Hospital during the last decade. As a simple method of evaluating the function of the treated hip so that it might be compared with that of the patient's normal hip, we used a modified Ferguson-Howorth "index of motion" table.

Thus we appraised function in 3 cases of marked slipping in which osteotomy was done at a point distal to the site of the deformity, i. e., distal to the epiphysal plate. The results were uniformly poor (table 1)—in fact, the poorest results of the entire series. We feel this method for the treatment of a patient with a slipped epiphysis should be discarded. It might be reserved for those with old traumatic arthritis and deformity, who could be helped by alteration of the mechanics of the hip joint.

The present treatment, arthrotomy of the hip joint, reposition of the displaced epiphysis on the neck and fixation by means of a three-flanged nail, followed postoperatively by traction and the wearing of non-weight-bearing splints, should be

continued for patients with marked slipping of the epiphysis. The group treated thus showed hip function 76.8 per cent of normal (table 2). This contrasts favorably with a comparable group treated by miscellaneous methods, such as osteotomy distal to the epiphysial plate, whose hip function was only 37.4 per cent of normal.

Lateral nailing in situ, without arthrotomy and without correction of the early deformity, is the best method of treatment for patients with only minimal slipping of the epiphysis, and this in spite of the good results obtained from drilling and traction. We have seen 2 hips with minimal slips left untreated except for the use of non-weight-bearing splints continue to slip to a marked degree. Since drilling and traction do not immobilize the epiphysis any more than a non-weight-bearing splint, we advocate lateral nailing in situ. Such a procedure demands no more skill of the surgeon and entails no more risk on the part of the patient than does the drilling operation. Lateral nailing is a relatively simple procedure for the surgeon who has been adequately trained. But if minimal slipping is allowed to progress, open reduction and nailing become necessary. This is a relatively difficult procedure even in the hands of the orthopedic surgeon. The results from arthrotomy, reduction and nailing, averaging 76.8 per cent of normal hip function, are not as good as the results from lateral nailing in situ. The latter method of treatment afforded by far the most gratifying results, averaging 94.8 per cent of normal hip function. This is also better than the 87.6 per cent for drilling and traction.

We therefore wish to stress the importance of diagnosing the condition early, while the slip is still minimal, of obtaining early fixation by lateral nailing in situ, of mobilizing the hip early after operation, and of recognizing early a possible slip in the contralateral hip.

## ADVENTITIOUS BURSAS

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Bursas have been defined as the synovial strata which are found outside of joints to reduce friction.<sup>1</sup> Normally they are located between the skin and bony projections and between tendons and prominences over which the tendons move.<sup>2</sup> Albinus,<sup>3</sup> while he was not the first to discover these synovial sacs, described their occurrence between muscles and gave them the name *bursae mucosae*. The normal bursas about the joints develop as a rule during the latter half of intra-uterine life. Complete maturation of the bursal cavity and definition of its outline are believed to come only with fetal movement. Occasionally, normal bursas develop first in early childhood, and instances have been reported in which even the larger bursas were not present in adult life.<sup>4</sup>

In addition to the usual bursas about the joints present at birth, other bursas develop not infrequently beneath the skin or about the tendons to prevent excessive friction or to protect from pressure. These bursas which develop after birth in unusual locations have been called adventitious bursas (fig. 1). A clearer understanding of the changes taking place in the tissues during the formation of such adventitious bursas will help the physician to appreciate the changes of connective tissue in response to unusual functional demands in all parts of the body. The adaptation of the tissues about transplanted tendons and where an attempt is made to regain articular motion is partially the formation of a number of such adventitious bursas.<sup>5</sup> The description of the clinical and histologic development of these bursas is the purpose of this paper.

Before the embryologic studies of Hagen-Torn,<sup>6</sup> it was believed that all bursas were lined with endothelium.<sup>7</sup> But the careful histologic studies of Hammar<sup>7</sup> and of Redderer<sup>8</sup> have demonstrated that the synovial lining both of joints and of bursas is only a special arrangement and modification of connective tissue cells.<sup>9</sup> This adaptation of the lining membrane of the cavity has been carried out to a greater degree in joints which have proceeded through a slower and more elaborate embryologic development than have bursas. All bursas, both the normally occurring and the adventitious ones, vary greatly in the completeness of the adaptation

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3. Albinus, B. S.: *Historia musculorum hominis*, Leido Batavorum, T. Haak et H. Mulhovijs, 1734.

4. MacDonald, H. K.: *Bursitis*, *Canad. M. A. J.* **40**:573, 1929.

5. Campbell, W. C.: *Surgery of the Hip Joint from the Physiologic Aspect*, *Surgery* **7**:165, 1940.

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7. Hammar, A.: *Ueber die feineren Bau der Gelenke*, *Arch. f. mikr. Anat.* **43**:266, 1894.

8. Redderer, E.: *Sur le development morphologique et histologique des bourses muqueuses*, *J. de l'anat. et physiol.* **32**:25, 1896.

9. Key, J. A., in Cowdry, E. V.: *Special Cytology*, ed. 2, New York, Paul B. Hoeber, Inc., 1932, p. 737.



of the inner lining of the bursal wall.<sup>10</sup> Some bursal cavities have a definite synovial membrane with cells like epithelial cells; others show somewhat flattened, undifferentiated connective tissue cells. More readily in the bursa of more undifferentiated connective tissue, but in that with true synovial membrane as well, regeneration of the lining membrane can take place after injury or after removal of the bursa.<sup>11</sup> This regeneration of the living cells takes place only if there are movement and intermittent pressure; without these obliteration of the bursal cavity occurs.<sup>12</sup>

Many studies have been made on normally appearing bursas which have been removed because of irritation or infection. The embryologic development of normal bursas, particularly those found about the shoulder joint, has been studied by Redderer<sup>8</sup> and more recently by Simon<sup>13</sup> and by Black.<sup>14</sup> In the human embryo the first sign of the developing bursa is a decrease in the number of fibrils in the primordial connective tissue. There occur a flattening and a conden-



Fig. 1.—Large adventitious bursa projecting along the lateral side of the fifth metatarsal bone.

sation of the collagen fibers. These changes are followed by the appearance of an intercellular space. Intercellular vacuoles then appear which suggest liquefaction within the cells. Gradually a cavity forms which is surrounded by collagen fibers. These fibers, probably from pressure, become parallel to the wall of the cavity. The sparsely distributed nuclei of the connective tissue cells become ovoid and later flattened along the inner wall of the bursal cavity.

With movement of the embryonic limbs, the bursa becomes more clearly defined. The wall, which at first is relatively thin, becomes thicker, and the inner lining takes on more of the appearance of a synovial membrane. Fetal movement

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12. Burrows, H. J.: Bursae and Ganglia, *Practitioner* **148**:50, 1942.

13. Simon, S.: Ueber Schleimbeutelformen am Schultergelenke des Menschen, *Ztschr. f. d. ges. Anat.* **81**:369, 1926.

14. Black, M.: Prenatal Incidence Structure and Development of Some Human Synovial Bursae, *Anat. Rec.* **60**:333, 1934.

is probably not essential for the formation of the bursa, but it is doubtful whether the latter ever attains full development without the stimulus of pressure and movement.<sup>15</sup> With movement, the connective tissue cells and the collagen fibers become arranged in the bursal wall and the secretion of mucin, or mucin-like substances, is initiated. With pressure, the wall thickens. Through normal growth or by the formation of adhesions the bursal cavity often becomes multilocular. Large bursas usually consist of a number of divided cavities.<sup>16</sup>

This manner of development has been observed for the bursas which are present at birth. While little study has been made of adventitious bursas, many theories and much speculation have appeared, connected with their formation. Virchow<sup>17</sup> and many subsequent investigators<sup>18</sup> have expressed the belief that trauma or severe irritation leads to necrosis and liquefaction of the connective tissue and that the bursal wall is a secondary formation about the fluid. Such proteolytic digestion and liquefaction of tissues<sup>19</sup> do take place at times, after injury, but no bursal formation is observed. Schuchardt<sup>20</sup> taught that adventitious bursas represented merely inflammatory production of cystic new tissue. Their relationship<sup>21</sup> to ganglions both in mode of formation and in histologic structure has been mentioned frequently. They have been confused with lymphatic hygroma<sup>22</sup> and have been regarded as dilatations of existing lymphatic channels. Interfascial hemorrhages which do not absorb have been mentioned as possible precursors of bursas.<sup>23</sup>

Attempts to produce adventitious bursas in laboratory animals have been entirely unsuccessful. The application of mild constant pressure on the skin overlying bony prominences in rats or rabbits has invariably led to necrosis of the tissues if sufficiently long continued, never to bursal formation. Intermittent pressure cannot be applied to exactly the same area nor can the pressure be repeated often enough to stimulate the formation of a bursa except in horses, which have shown adventitious bursas under badly fitting collars and saddles. Injections of bland oily substances which were not absorbed have given the temporary appearance of bursal cavities with formed walls; but these cavities were soon replaced by scar tissue, and no true bursal wall was formed.

The formation of adventitious bursas can best be observed in human beings who continue to wear badly fitting shoes or improperly adjusted apparatus. In a clinic largely devoted to disabilities of the feet, an excellent opportunity was provided for the study of adventitious bursas in all stages of development from slight redness and thickening of the skin to the completely formed bursa with its complications of infection, hemorrhage and intrabursal osteocartilaginous bodies. Removal of tissue at operations for the correction of disabilities of the feet permitted histologic examination of a number of these bursas, which provided correlation with the clinical observations. The histologic observations of this study

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16. Martin, B.: *Ueber künstliche und erworbene Schleimbeutel und ihre Beziehungen zu den Gelenken*, Arch. f. klin. Chir. **120**:281, 1922.

17. Virchow, R.: *Die krankhaften Geschwülste*, Berlin, A. Hirschwald, 1863.

18. Ricker, G.: *Die Verflüssigung der Bindegewebsfasern zugleich ein Beitrag zur Kenntnis der fibrinoiden Degeneration*, Virchows Arch. f. path. Anat. **163**:44, 1900.

19. Wells, H. G.: *Chemical Pathology*, Philadelphia, W. B. Saunders Company, 1920.

20. Schuchardt, K.: *Ueber die Entstehung der subcutanen Hygrome*, Arch. f. klin. Chir. **40**:606, 1890.

21. Carp, L., and Stout, A. P.: *A Study of Ganglion*, Surg., Gynec. & Obst. **47**:410, 1928.

22. Tow, A.: *Cystic Hygroma in Infancy*, Arch. Pediat. **58**:73, 1941.

23. Serrel, E.: *Hygroma hémorrhagique de la bourse séreuse du psoas*, Bull. et mém. Soc. nat. de chir. **55**:98, 1929.

were then compared with those from the further study of a large number of specimens of pathologic bursas and ganglions at the Boston Children's Hospital.

Clinical observations have shown that the formation of an adventitious bursa or the occurrence of irritating movement particularly over a bony prominence is dependent on oft-repeated mild pressure. Severe pressure applied once or constant pressure leads to hemorrhage or to necrosis of the tissues. The pressure or the irritation must be insufficient for the death of the tissue and must be often repeated for a long time for the development of a bursa, which is a relatively slow process. On the foot one first sees persisting redness of the skin, which is soon followed by callus. Beneath this callus a bursa is beginning to form, but it cannot be recognized in the tissues at this time. The palpation of a bursa is not possible for several weeks, and often the bursa cannot be found for several months. Continued irritation leads to an accumulation of fluid in the bursal cavity,<sup>24</sup> and this makes palpation easier.

Histologic study of tissues removed at operations in areas where adventitious bursas were developing or had fully developed permitted observation of the various stages in the formation of the adventitious bursa. The first change observed in the subcuticular connective tissue was a localized thickening of the relatively loose areolar tissue, similar to a mild inflammatory reaction but without leukocytic infiltration. Following this early response, the connective tissue fibers assumed instead of the usual irregular arrangement a position parallel to the pressure exerted on the skin (fig. 2). These bundles of connective tissue fibers gradually showed a flattened, wall-like surface which at first was only several cells thick but became thicker under continued pressure. In the surrounding fatty and areolar tissue hemorrhage and edema were often observed.<sup>25</sup> After this stage, a cavity containing fluid began to appear.

In this cavity there was always one parallel fissure with several radiating fissures. As these fissures enlarged, a bursal cavity was formed. Adventitious bursas were never seen developing in preformed spaces in the connective tissue.<sup>26</sup> Martin<sup>27</sup> observed that connective tissue loses its elasticity and tears readily when subjected to repeated trauma. A bursal cavity could occur in such tears in connective tissue fibers, but it is more probable that the bursal wall forms about an accumulation of fluid beneath the area of pressure. The connective tissue cells subjected to irritation frequently show vacuoles suggesting secretory activity.

Whether the fluid which is found at first in an adventitious bursa is tissue fluid or whether it contains mucin from the beginning is difficult to determine.<sup>28</sup> Tests have shown the presence of a mucin-like substance in the fluid of the adventitious bursa at all stages in which examination was made. This suggests that a mucin-like substance appears fairly early in bursal development. Mucin, a compound protein with conjoined sulfuric acid,<sup>29</sup> is found in the body chiefly in two locations: on the surface of epithelial cells, as a secretion, and in the interstices of connective tissue. Mucin and related compounds provide the viscosity and lubricating action of the bursal fluid. This bursal fluid contains in addition to the

24. Tubby, A. H.: Clinical Lecture on Chronic Enlargement of Bursae, *Clin. J.* **15**:313, 1899.

25. Toussaint, H.: Exostoses mobiles et bursite traumatique de la patte d'oie, *Rev. d'orthop.* **6**:53, 1905.

26. Anderson, W. S.: A Study of the Normal and Pathological Conditions of the Bursae of the Neck with Special Reference to the Subhyoid Bursa, *Am. J. M. Sc.* **127**:439, 1904.

27. Martin, B.: Ueber Spalt und Höhlenbildung primäre Hohlraum-bildung oder Gewebeverflüssigung, *Virchows Arch. f. path. Anat.* **228**:384, 1920.

28. Mommsen, E.: Zwei Fälle gutartiger grosser Schleimbeutelhygrome, *Deutsche med. Wchnschr.* **20**:107, 1894.

29. Levene, P. A., and López-Suárez, J.: Mucins and Mucoids, *J. Biol. Chem.* **36**:165, 1915.

mucin-like substance a small amount of protein and salts which probably come as a dialysate from the capillaries surrounding the bursa.<sup>30</sup>

It is believed that all connective tissue cells can produce mucin under the appropriate functional stimulus. Garrault<sup>31</sup> observed that all tissue originating from mesenchyme was characterized by the ability to elaborate intracellular sub-

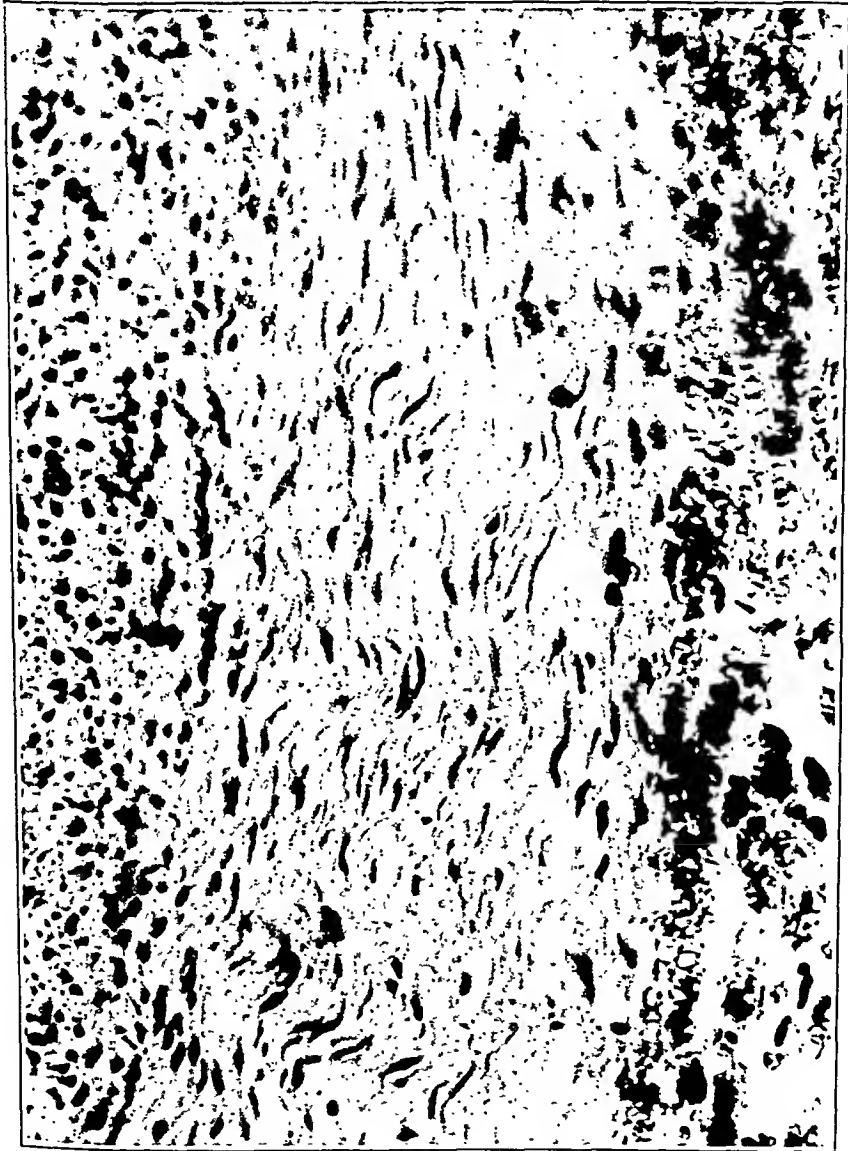


Fig. 2.—Photomicrograph of the tissues beneath a callus on a foot;  $\times 622$ . There is hemorrhage in the superficial tissues. The connective tissue cells and the collagen fibers are flattened and arranged in parallel bundles. In two central areas with loose intercellular material are the antecedents for bursal formation.

30. Ropes, M. W.; Bennett, G. A., and Bauer, W. A.: Origin and Nature of Normal Synovial Fluid, *J. Clin. Investigation* 18:351, 1939.

31. Garrault, H.: Étude histochimique de quelques tissus conjonctifs muqueux, *Arch. d'anat. micr.* 30:6, 1934.

stances into a viscous jelly-like compound. In the neighborhood of certain rapidly growing tumors a liquefaction of connective tissue, the so-called mucoid degeneration, is observed. This is interpreted to be a reversion to the fetal type of tissue with the response which is characteristic of fetal tissues.<sup>10</sup>



Fig. 3.—Early adventitious bursa removed from the first metatarsophalangeal joint;  $\times 222$ . The wall of the bursa is thin and shows no definition of an inner cellular layer.

In bursas the mucin is elaborated, probably secreted, by the flattened connective tissue cells lining the bursal wall. Kling<sup>32</sup> was able to demonstrate the precursors of mucin in vacuoles in connective tissue cells about joints by staining with

32. Kling, D. H.: *The Synovial Membrane and the Synovial Fluid*, Los Angeles, Calif., Medical Press, 1938.

toluidine blue. From cultures of synovial membrane Vaubel<sup>33</sup> concluded that the cells of the synovial membrane have developed the ability to form a synovial fluid and mucin to a special degree and that they differ greatly from other connective tissue cells.

After an adventitious bursa has formed, it is subject to the same pathologic changes that occur in the normally appearing bursa. As the bursal wall becomes thicker, villous formation begins.<sup>34</sup> This greatly increases the secreting surface of the bursa. The lining membrane of the bursa may eventually become a true synovial membrane, but this degree of development in an adventitious bursa is not commonly seen.<sup>35</sup> Infection is relatively common in adventitious bursas, especially in those of the hands and feet, where trauma often occurs. This infection is rarely virulent and seldom is followed by a serious systemic reaction.<sup>36</sup> In the presence of infection there may be a slight purulent discharge. Following such infections, the bursal cavity is occasionally obliterated and is gradually replaced by scar tissue. Great enlargement of an adventitious bursa may occur with persistent irritation and trauma.<sup>37</sup> One patient had a bunion over the first metatarsophalangeal joint which, through prolonged irritation, enlarged until it covered the entire lateral and inferior surface of the great toe. Rupture of a bursa is uncommon. In certain locations where enlargement of a bursa is difficult because of its ligamentous attachments, thickening and infolding of the bursal wall may occur (fig. 4).

Less common pathologic involvements are tumor formation and tuberculous infection. Synovial sarcoma is described in bursas by Berger.<sup>38</sup> There are two types, one arising from ordinary fibrous tissue and the other from more differentiated synovial cells with reticulohistiocytic meshwork.<sup>39</sup> Xanthoma-like growths have been found in bursas by Jaffe, Lichtenstein and Sutro,<sup>40</sup> who considered them to be inflammatory rather than neoplastic in nature. With long irritation as well as with chronic infection, osteocartilaginous bodies may form in bursas.<sup>41</sup> They arise by metaplasia of cells or in an attempt at repair<sup>42</sup> by cells in the villi of the bursal walls (fig. 5). Tuberculous infection in bursas has been described by Wassersug<sup>43</sup> and syphilitic infection by Churchman.<sup>44</sup>

Subcutaneous connective tissue will produce an adventitious bursa under the stimulus of repeated mild trauma, and the removal of that repeated trauma will often lead to regression and sometimes to complete disappearance of the bursa.

33. Vaubel, E.: Form and Function of Synovial Cells in Tissue Cultures, *J. Exper. Med.* 58:63, 1933.

34. Fisher, A. G. T.: *Chronic (Non-Tuberculous) Arthritis*, New York, The Macmillan Company, 1929.

35. Jones, H. T.: Cystic Bursal Hygromas, *J. Bone & Joint Surg.* 12:43, 1930.

36. Pick, H.: Zur Frage der Infektiosität der Schleimbeutel beim Hallux valgus, *Zentralbl. f. Chir.* 54:70, 1927.

37. Broster, L. R.: Bursitis, *Brit. M. J.* 2:1006, 1929.

38. Berger, L.: Synovial Sarcoma in Serous Bursal and Tendon Sheaths, *Am. J. Cancer* 34:501, 1938.

39. Franceschini, P.: Recherche istologiche sulle articolazioni, *Arch. ital. di anat. e di embriol.* 27:76, 1929.

40. Jaffe, H. L.; Lichtenstein, L., and Sutro, C. J.: Pigmented Villonodular Synovitis, Bursitis and Tenosynovitis, *Arch. Path.* 31:731 (June) 1941.

41. Ettore, E.: Ueber die Bildung von freien Körpern bei Exostosis bursata, *Ztschr. f. orthop. Chir.* 50:113, 1929.

42. Schwarz, E.: Untersuchungen über die Entstehung der Zotten und Reiskörper in Hygromen, *Deutsche Ztschr. f. Chir.* 235:140, 1932.

43. Wassersug, J. D.: Tuberculosis of the Greater Trochanter and the Trochanteric Bursae, *J. Bone & Joint Surg.* 22:1075, 1940.

44. Churchman, J. W.: Luetic Bursopathy of Verneuil, *Am. J. M. Sc.* 138:171, 1909.

This is observed best in small bursas such as those which form superficially about the foot.<sup>45</sup> Here with removal of the irritation the bursa becomes smaller, and finally no further evidence of it can be found. In the thick-walled larger bursas complete obliteration is rarely seen. But with removal of the traumatic stimulus nature will attempt to remove a structure that is no longer required. Week by

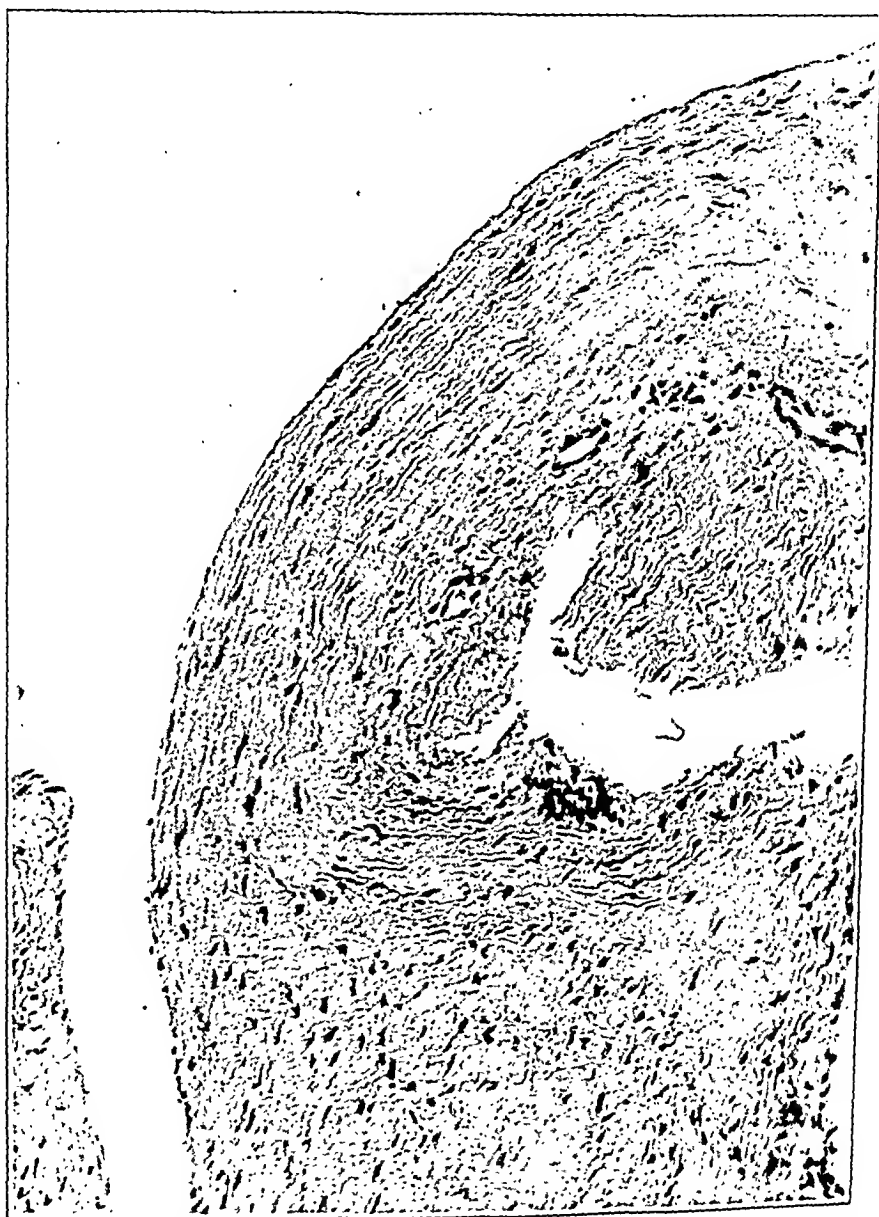


Fig. 4.—Very old bursal wall which has been chronically infected;  $\times 311$ . The wall is very thick and shows fissure formation. The bursa is limited by flattened connective tissue cells.

week one can see a gradual decrease in the size of the bursa. In several months often no bursa can be palpated. But a thickening of the tissues in the bursal area can usually be felt for an indefinite period. If pressure and irritation

45. Galland, W. L.: Operative Treatment of Corns, *J. A. M. A.* 100:880 (March 25) 1933.

are again exerted over the area for several weeks, the bursa reappears and will soon return to its former size.

The histologic study of the involved tissues during the subsidence of an adventitious bursa shows the reverse of the process which is observed in its formation. The fluid in the bursa is gradually absorbed. The bursal wall becomes



Fig. 5.—Old adventitious bursa removed from the inner side of a foot;  $\times 266$ . There are villous formation and the beginning of a loose body from coagulum and cellular detritus. The lining cells simulate a true synovial membrane.

thinner; adhesions form between the two sides. This process is sometimes hastened by hemorrhage.<sup>46</sup> Hemorrhage or severe trauma is followed sometimes

<sup>46</sup> Hayward: *Chirurgisches Konsilium, Med. Klin.* 27:1759, 1931.



by calcification in the bursal wall.<sup>47</sup> The final stage will show only a thickening of the connective tissue, similar to a scar, in the area where the bursa has been. Occasionally this process of fibrosis<sup>48</sup> proceeds so irregularly that it leads to a chronically painful area.

Many attempts have been made to hasten the natural process of regression in adventitious bursas. Aspiration<sup>49</sup> with or without subsequent pressure over the area has been of little help in causing the bursa to disappear more rapidly. Rapid obliteration of the cavity comes only with destruction of the lining cells.<sup>50</sup> The simplest and most effective method is that of complete removal of the bursa. This is the treatment of choice at the elbow and the knee, where slow regression of the bursa would frequently interfere with normal use of the limb.<sup>51</sup> With the smaller adventitious bursa, the removal of the irritation or the pressure will usually lead to rapid relief of the symptoms<sup>52</sup> and to slower but complete disappearance of the bursa.

#### SUMMARY

Adventitious bursas are frequently observed in subcutaneous tissues that are subjected to repeated pressure or friction. The development of these bursas is similar to the embryonic development of the normally appearing bursas. There is condensation of the subcutaneous connective tissue followed by the development of a fluid-containing cavity. True synovial lining is not often found in adventitious bursas. A mucin-like substance is found early in the development of the bursas. It is apparently produced by the connective tissue cells lining the bursal cavity. The same pathologic changes which are found in the normally occurring bursa are seen in the adventitious bursa: infection, enlargement, tumor formation and fibrosis. With removal of the irritating stimulus, regression of the bursa is observed. Complete spontaneous disappearance of the smaller adventitious bursas often takes place. The larger bursas usually require surgical removal.

47. Pohl, R.: Zur Rückbildung von Kalkeinlagerungen in Schleimbeutel, *Wien. klin. Wchnschr.* **43**:1397, 1930.

48. Morris, M.: Clinical Notes on a Case of Fibroid Disease of Bursae, *Brit. M. J.* **1**: 867, 1917.

49. Pass, H. R., and Schüller, J.: Entstehung riesiger cystischer Tumoren durch Schleimbeutelruptur, *Zentralbl. f. Chir.* **57**:2425, 1930.

50. Sarma, P. J.: The Injection Treatment of Ganglions and Bursae: Indications and Limitations, *S. Clin. North America* **20**:135, 1940.

51. Reder, F.: Inflammation of the Prepatellar Bursa, *S. Clin. North America* **5**:1289, 1925.

52. Saxl, A.: Wie werden Schleimbeutelentzündungen des Fusses orthopädisch behandelt? *Wien. klin. Wchnschr.* **48**:929, 1935.

# FRACTURE OF THE SHAFTS OF BOTH BONES OF THE LOWER HALF OF THE LEG

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The main objectives in the treatment of a fracture are (1) the best possible end result and (2) the shortest period of disability consistent with such a result. The chief concern of the community at large and also of the patient is how long he will be disabled. Even in cases in which wage earning is not involved, as in those of school children, housewives, and aged persons, confinement and dependence on others are considerations of the first importance. The literature and hospital records are conspicuously lacking in data on when patients return to work or resume useful occupations.

Fracture of both the tibia and the fibula has become increasingly common with the development of the machine age, constituting 8 per cent of the fractures for which patients have been admitted to one representative municipal hospital. It is also one of the most disabling common injuries. Fracture of the shaft constitutes the majority of the fractures of the bones of the lower half of the leg and is selected for discussion.

The patients treated for fracture of the tibia and the fibula in Lincoln Hospital (Department of Hospitals, New York) during the three year period 1939-1941 inclusive numbered 176. Of these, 9 died, a mortality of 5.1 per cent.<sup>1</sup>

The series whose cases are reported here is composed largely of those patients from the group just mentioned whom we were able to follow, plus a similar group from the French Hospital and from private practice. A fairly typical cross section of the metropolitan population is represented. Children under 5 years are not included, as they can scarcely be considered from the point of view of disability.

A trend toward skeletal traction has been apparent during the past ten years. The use of pins and wires has developed in spite of some reluctance to accept the principle of the puncturing of skin and healthy bone. Traction through the calcaneus was later followed by distraction with pins drilled through both fragments and incorporated in plaster. Good results have been reported by Anderson,<sup>2</sup> Curry and Taylor,<sup>3</sup> Griswold<sup>4</sup> and others. Patients are ambulatory, hospitalization is shortened, and retention of fragments is efficient. There is danger, however, of nonunion from separation of fragments. Infection of bone from skeletal traction does occur but seems to be rare.

1. These figures are taken from an unpublished report of the record room of the Lincoln Hospital.

2. Anderson, R.: An Automatic Method of Treatment for Fracture of the Tibia and Fibula, *Surg., Gynec. & Obst.* **58**:530-646 (March) 1934.

3. Curry, G. J., and Taylor, E. S.: Fractures of Both Bones of Leg: Management by Use of Double Steel Pin Traction in Plaster of Paris, *Arch. Surg.* **36**:858-866 (May) 1938; correction, *ibid.* **37**:352 (Aug.) 1938.

4. Griswold, R. A.: Fracture of Both Bones of Leg: Treatment by Modified Boehler Method with New Apparatus, *J. A. M. A.* **104**:35-40 (Jan. 5) 1935.

Open reduction with internal fixation has been advocated particularly for spiral and oblique tibial fractures. The difficulty of maintaining reduction of these most common fractures of the bones in the lower half of the leg is proverbial. The

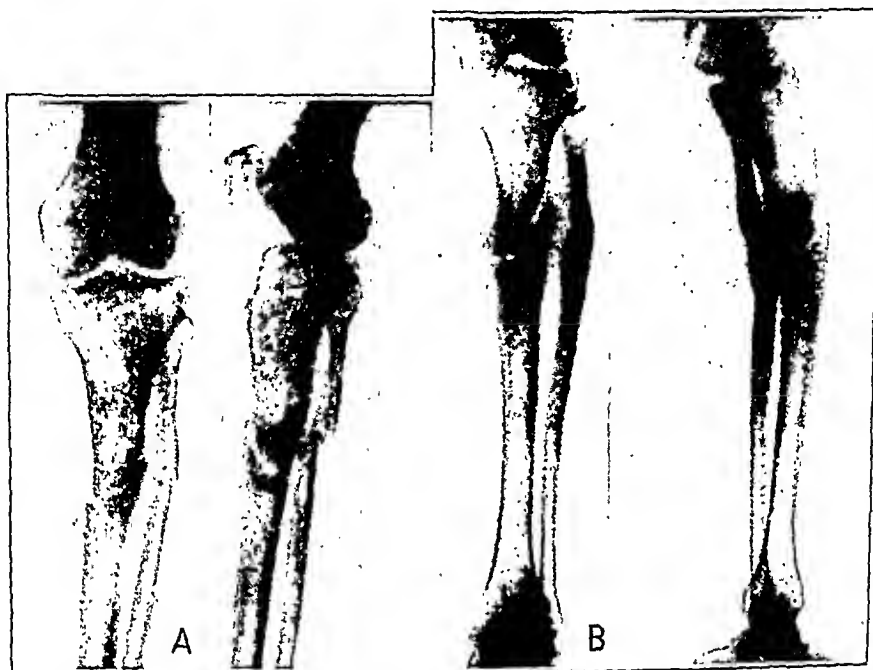


Fig. 1 (case 19).—*A*, tibia and fibula showing comminuted fracture in February 1939. *B*, same bones in November 1942. The fibular fragment and the free fragment of the tibia are united. There is fibrous union of the upper tibial fragment.

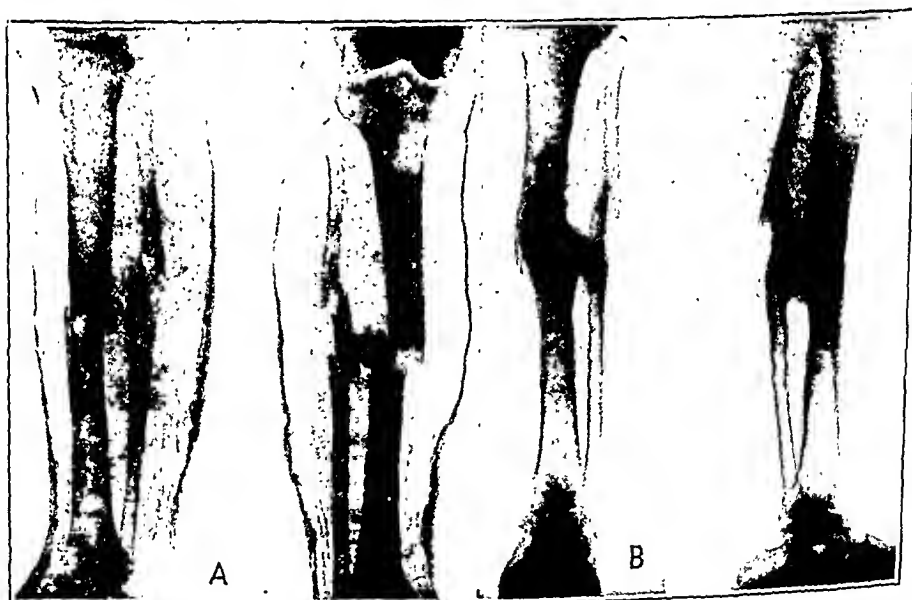


Fig. 2 (case 24).—*A*, marked comminution in August 1940. *B*, abundant callus and apparent cross union in October 1942.

problem of treating them by other means has not yet been solved. The frequency of nonunion and the accessibility of the shaft of the tibia are two of the considera-

tions in favor of open reduction. Mansfield<sup>5</sup> expressed the view that these fractures constitute a clinical entity and reported that the period of hospitalization and the period of disability were greatly reduced following immediate wiring. Closed methods seem to be still favored by the majority, however.

A modification of closed reduction has been used, with encouraging results. Two pins are introduced into each fragment if the fracture is not too near the end of the bone, and an adjustable side bar is used for fixation. The use of plaster

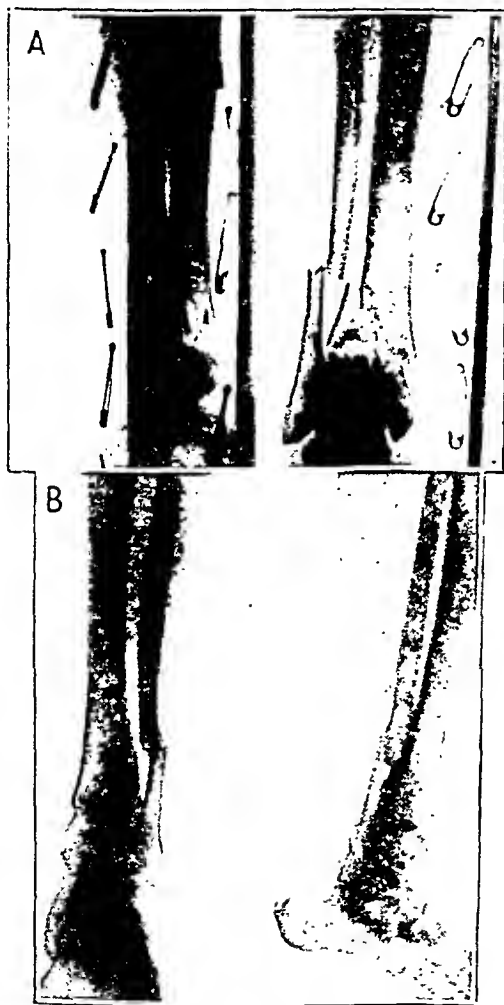


Fig. 3 (case 13).—A, lateral displacement and marked comminution in February 1941. B, good alignment and firm union in October 1942.

can be eliminated by this means, and much interest has recently been focused on the principles involved.<sup>6</sup>

5. Mansfield, R. D.: Treatment of Oblique Spiral Fractures of Both Bones of the Leg: Analysis of 15 Cases Treated by Open and Closed Methods, *J. Bone & Joint Surg.* **23**:910-916 (Oct.) 1941.

6. Bradford, C., and Wilson, P. D.: Mechanical Skeletal Fixation in War Surgery, *Surg., Gynec. & Obst.* **75**:468-476 (Oct.) 1942. Lewis, K. M.; Breidenbach, L., and Stader, O.: The Stader Reduction Splint, *Ann. Surg.* **116**:623-636 (Oct.) 1942.

In our series of 32 cases manipulation with plaster immobilization was used only nine times. The group thus treated included all but one of the youngest patients, and most of the shortest periods of disability were recorded for this group. The brevity of the periods of disability is obviously due to the adaptability of growing bones and to the lack of gross deformity in the patients so treated.

Recumbency with Kirschner wire traction through the calcaneus was used in 17 cases, or a little more than 50 per cent. The wire was left in place on an average of nearly four weeks and was replaced by plaster splints when union was firm enough or was incorporated in plaster for ambulatory treatment. Compounding or associated injuries, including shock, were present in 10 of these cases. Many of the longest periods of disability and poorest results were found in this group comprising the most seriously injured patients.



Fig. 4 (case 1).—*A*, technical error in the reduction of a fracture in June 1937. Such errors are still seen occasionally. *B*, same bones in November 1942. Any benefit from this operation was probably due to stimulation from the drill hole.

Among those of particular interest was a 54 year old housewife, injured in an automobile accident, with multiple fractures of rib and injury of the head besides the fractures of the bones in her leg. Although she had fibrous union only of the tibia (fig. 1), she considered herself no longer disabled at the end of one year and showed good function of the knee and the ankle. There were outbowing and limp (case 19 in table).

A 50 year old laborer, also the victim of an automobile accident, sustained a compound fracture of the bones in the lower half of the right leg, with a persistent draining sinus (fig. 2). The cross union shown in figure 2 *B* has rarely been encountered in our experience but is of little clinical significance. In spite of complications, the patient after ten months walked with slight limp and did light work, though he was not able to continue steadily (case 24).

A 56 year old laborer fell and sustained a badly comminuted fracture of the lower third of the tibia and the fibula of the left leg (fig. 3). His convalescence was complicated by serious phlebitis and pulmonary infarction. The course of illness was stormy, and the patient was still disabled one and a half years after the accident, though union was firm and weight bearing with a bandage was fair (case 13).

Open reduction was performed six times.

A 37 year old Negro woman sustained an oblique fracture of the middle and lower thirds of the right tibia (fig. 4). She had asthma with cardiac complications. An attempt was made to fix the fragments with a single screw, a violation, admittedly, of the principles of internal fixation. Although some shortening and angulation occurred, the bones showed firm union and good functional result after seven months' disability (case 10).

A 34 year old saleslady slipped in the street, sustaining a compound spiral fracture of the lower third of the left tibia, which was immediately operated on (fig. 5). A Parham band

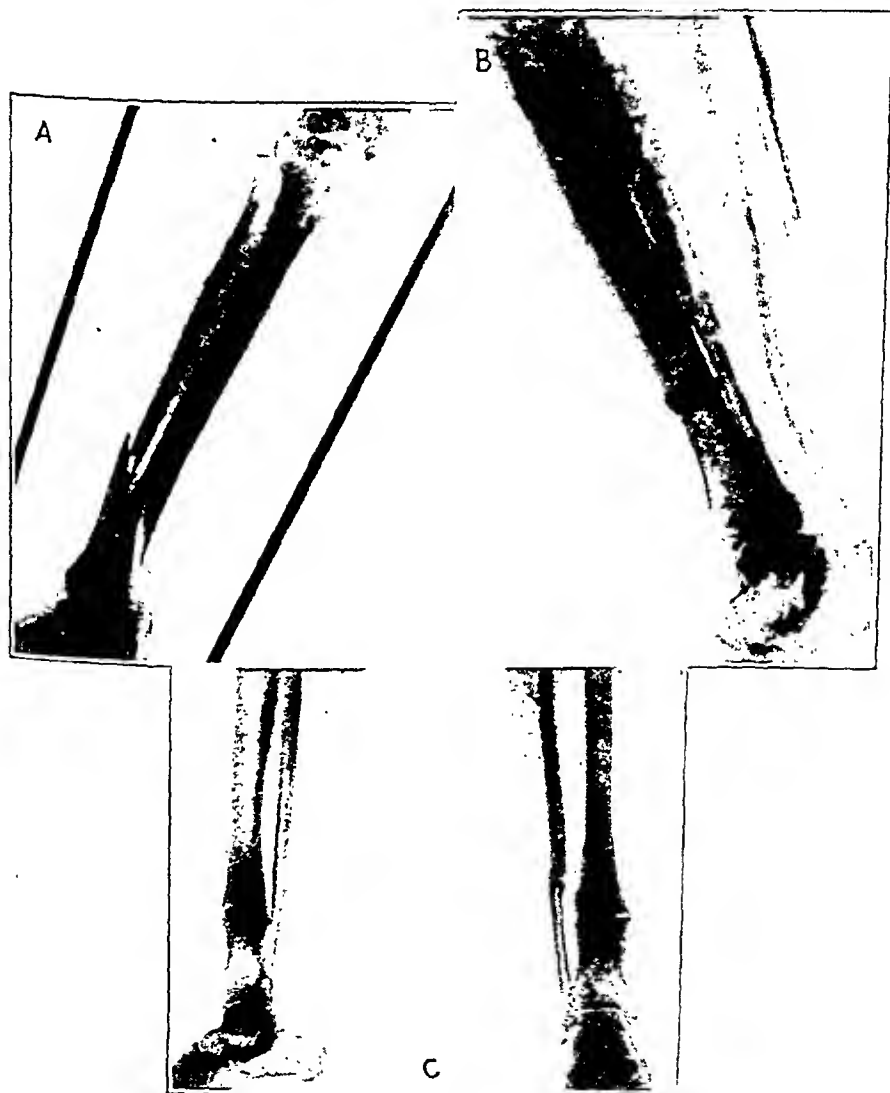


Fig. 5 (case 11).—*A*, typical spiral fracture in February 1941. *B*, Parham band fixation. *C*, same bones in November 1941. The surprising superabundant callus raises the question of incomplete immobilization or foreign body reaction.

was used with accurate reduction, and there was good convalescence with a total of fifteen days' hospitalization. Bony proliferation caused objectionable thickening of the ankle but within seven months she returned to work with good function of the ankle (case 11).

Lane plates were used in the treatment of 2 patients. One had compounding, and a sinus developed, necessitating the removal of the plate after callus was

# Analysis of Data on Thirty-Two Patients Treated for Fracture of Both Tibia and Fibula

No.	Age and Sex	Cause	Treatment	Days in Hospital	Complications	Disability	Deformity	S A E*	Comment
1	48 F	Fall	Open operation; metal screw	52	Cardiac asthma	7 mo.	Lateral bowing	4 3 4	Clinically good position
2	46 F	Fall	Kirshner wire	69	Congenital dislocation of hip	12 mo.	Swelling	2 3 2	History of hypertension
3	19 M	Automobile accident	Debrided; Kirshner wire	57	Compounding	13 mo.	None	3 4 4	In army after 1 year
4	8 M	Automobile accident	Plaster	42	Compounding	3½ mo.	None	4 4 4	Callus after 15 days
5	68 M	Automobile accident	Kirshner wire	35	.....	4 mo.	Lateral angulation	3 3 3	No limp; does light work
6	10 F	Fall	Plaster	27	.....	2 mo.	.....	4 4 4	
7	5 M	Fall	Plaster	3	.....	4 mo.	.....	4 4 4	
8	75 M	Automobile accident	Kirshner wire	51	Injury of head; diabetes	10 mo.	Swelling, lateral bowing	2 2 3	Good recovery despite age of 75 years
9	6 M	Fall	Plaster	3	.....	7 wk.	.....	4 4 4	
10	13 M	Automobile accident	Plaster	41	Phlebitis; Colles' fracture	3 mo.	.....	4 4 4	
11	5 F	Automobile accident	Plaster	21	.....	7 wk.	.....	4 4 4	
12	13 M	Fall	Plaster	12	.....	2½ mo.	.....	4 4 4	
13	56 M	Fall	Kirshner wire	60	Phlebitis	17 mo.	Swelling	2 3 1	Pain; still disabled after 1½ yr.
14	5 F	Automobile accident	Debrided wire	90	Compounding, sloughing	8 mo.	Scar, bowing	4 2 4	Severe injury of bone and soft parts
15	58 M	Jump	Kirshner wire	150	.....	11 mo.	Swelling	4 3 4	Two admissions; occasional pain in heel
16	51 F	Fall	Kirshner wire in plaster	28	.....	3½ mo.	None	4 4 4	Skeletal traction and plaster immobilization combined
17	38 F	Fall	Kirshner wire	34	.....	6 mo.	Anterior bowing	1 2 3	Pain and edema; sedentary occupation
18	44 M	Automobile accident	Plaster	28	Wound of scalp	5 mo.	.....	4 4 4	Standing; elevator operator
19	54 F	Automobile accident	Kirshner wire	45	Fracture of ribs; wound of head; erysipelas	1 yr.	Anterior and lateral bowing	2 2 2	Pain in leg; fibrous union
20	65 F	Automobile accident	Kirshner wire	54	Compounding	2 yr.	Lateral bowing	1 1 1	Pain and limp; disabled
21	55 M	Automobile accident	Kirshner wire	365	Compounding shoe; fracture of arm	4 yr.	Shortening	1 1 0	Clinically good union; sequestration
22	21 M	Fall	Kirshner wire	65	Compounding	1 yr.	None	3 3 3	Discharged after 2 mo. in army
23	37 F	Fall	Lane plate	63	.....	7½ mo.	Swelling	3 4 3	Some pain; overweight; litigation
24	50 M	Automobile accident	Kirshner wire	48	Compounding	10 mo.	Deformity	3 1 2	Sequestration; still disabled
25	44 M	Fall	Kirshner wire	61	Concussion; pneumonia	8½ mo.	Swelling	3 3 4	Some pain in back and leg
26	57 M	Fall	Plaster Kirshner wire	95	Compounding, osteomyelitis	11 mo.	None	3 3 4	Knee flexes to 90 degrees
27	16 M	Football injury	Plaster	10	.....	2 mo.	None	4 4 4	
28	37 M	Automobile accident	Kirshner wire	43	Concussion	18 mo.	.....	1 1 1	Pain and stiffness; disabled
29	19 M	Football injury	Kirshner wire	27	.....	5 mo.	None	4 4 4	Joined navy 10/22/42
30	67 F	Automobile accident	Open reduction; plaster	96	Compounding; shoe; injury of head	9 mo.	Overriding	3 3 3	Improving; wears brace
31	34 F	Fall	Open operation; Parham band	15	.....	7 mo.	Swelling	3 4 4	Overweight; litigation
32	48 M	Automobile accident	Lane plate	111	Compounding; osteomyelitis	14 mo.	Bowing	3 3 3	Disabled; litigation

\* In these three columns symptomatic (S), anatomic (A) and economic (E) disability is graded from 1 to 4, with 4 representing the maximum degree.

shown by the roentgenogram. The other had a simple oblique fracture which failed to give a satisfactory reduction with manipulation and plaster. She returned to work with the plate in situ seven and one-half months after injury. Both made good recoveries but were involved in litigation, which frequently is prejudicial to periods of disability.

Silver wires were used in the case of a 5 year old girl who was struck by an automobile, sustaining a badly comminuted fracture of the middle third of the tibia, which sloughed extensively. Removal of the wires became necessary. With a skin graft a good functional result was obtained, thanks to the reparative powers of youth. Weight bearing was begun, and walking without limp, one year after the accident (case 14).

A middle-aged professional woman sustained a compound fracture of the lower third of the right leg, with concussion and injury of the head. Debriding and suture were followed by union in three months; weight bearing and some earning capacity were present at nine months. At the time of writing, fourteen months after the accident, she can stand and walk short distances with a cane and wearing a leg brace (case 30).

#### *Averages and Totals*

Average age .....	36.6 yr.
Average period of disability.	5.7 mo.
Average stay in hospital...	10.2 days
Cases in which compound fracture was observed	10, or 31.2%
<b>Causes</b>	
Fall.....	14 cases, or 43.7%
Automobile accident.	15 cases, or 46.9%
Other mishaps....	3 cases, or 9.4%
<b>Treatment</b>	
Kirschner wire ...	17 cases, or 53.1%
Plaster...	9 cases, or 28.1%
Open .....	6 cases, or 18.8%

In evaluating these results one notes three fundamental factors becoming increasingly clear:

1. The mental endowment of the patient and the nature of the occupation were of great importance. One patient who failed to return to work was on relief before he was injured, and his general makeup limited the employment available to him. Another, who had his own tailor shop, returned to work after eight months although he had sustained concussion and contracted pneumonia during convalescence.

2. Associated injuries and complications, especially vascular trauma and cardiovascular conditions, prolonged disability and impaired end results.

3. Compensation and medicolegal claims are too well recognized to require further comment. Some of the patients who walked without limp and showed good functional results remained out of work pending settlement of their cases in court or as long as compensation was continued.

#### SUMMARY AND CONCLUSIONS

Thirty-two cases of fracture of the shafts of the tibia and the fibula in which various methods of treatment were followed are presented.

The periods of disability of those who returned to work averaged five and seven-tenths months.



Marked improvement in methods and in results of treatment has been observed over the last ten years.

Skeletal traction can be used with reasonable safety and with expectation of good results.

Open reduction is indicated in selected cases.

End results are difficult to evaluate, and length of disability is not an accurate index of the efficiency of the method of treatment or of the severity of the injury.

Of the 6 patients who had not returned to work when last seen, 3 have the poorest results recorded—four years, two years and one and one-half years, respectively, after injury. All 3 patients showed bony union, but in 2 there was chronic osteomyelitis.

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# DEVELOPMENT OF THE HUMAN KNEE JOINT

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My interest in developmental and acquired pathologic disturbances of the menisci of the knee joint prompted me to seek an answer to the variations seen. I was desirous chiefly of learning the origin and time of appearance of the menisci and of the synovial membrane and their relationship to one another. The current textbooks and available literature were inadequate and confusing on these points because of widespread disagreement among various authors. The concept of the development of the knee joint varied according to the approach, whether from the point of view of embryology or that of comparative anatomy. The present study is based on embryologic observations and study of human anatomic specimens alone.

## COMPARATIVE ANATOMY

In 1887 Sutton<sup>1</sup> explained the origin of the intra-articular structures by the indrawing of extra-articular ligaments with the assumption of ability to flex the joint. The menisci were said to be derived from the femorocaudal and associated muscles by the mechanism he suggested.

Certain mammals, such as the beaver, Ungulata, Edentata and Monotremata, have knee joints made up of three compartments, and cavities of this type have been encountered in man.<sup>2</sup> The ligamentum mucosum and the alar ligaments as seen in the usual human specimen are considered to be the remains of the wall separating the patella and the femoral condyles.

The anterior cruciate ligament and the ligamentum mucosum are not separated in the lower monkeys as they are in man.<sup>3</sup> *Macacus rhesus* has an internal meniscus like that of man, but the external meniscus is continued obliquely across the joint behind the posterior cruciate ligament to the internal femoral condyle. In man the posterior part of the external meniscus is firmly attached to the tibia, but it gives off a structure known as the ligament of Wrisberg, which in turn is attached to the femoral condyle so that the difference between the two species is not very marked. In all joints of the mammalian type the menisci are attached to the femurs rather than to the tibias. The added fixation noted in man has been thought to be present in order to bear the added strain of standing with the knees in extension.

The external meniscus of the baboon, the vervet and the spider monkey and of the monotreme is ring shaped while the medial one is crescentic. This configu-

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1. Sutton, J. B.: Ligaments: Their Nature and Morphology, Philadelphia, P. Blakiston, Son & Co., 1887.

2. Struthers: Complete Septum in the Femoro-Tibial Part of the Knee Joint, *J. Anat. & Physiol.*, vol. 27, pt. 3, 1893.

3. Parsons, F. G.: The Joints of Mammals Compared with Those of Man, *J. Anat. & Physiol.* 34:301 (April) 1900.

ration is also seen rarely in man. Both menisci of the long-eared bat (*Plecotus*) are ring shaped. No menisci have been found in those animals whose knees have no power of rotary motion, such as the fruit bat (*Cheiroptus*).

The most primitive arrangement of menisci is that in which both are attached posteriorly to the femur as in the duck mole and the anteater. Other mammals show attachment of the external one to the femur posteriorly and of the internal one to the tibia; however, in man both are fixed posteriorly to the tibia.

In all monkeys and monotremes the superior tibiofibular joint communicates with the knee joint, but this feature is not seen in Insectivora and has not been reported among many types of anomaly seen in man except as stated by Sir Arthur Keith.<sup>4</sup>

#### LITERATURE.

The general lack of detail and the striking variance of opinion are well illustrated by the data presented in the following literature.

In Gray's "Anatomy of the Human Body"<sup>5</sup> it is stated that in several diarthroses the mesoderm between the ends of the bones does not become absorbed completely, a portion persisting and forming articular disks, but no details are available beyond these statements.

Arey<sup>6</sup> stated that the ligaments and the tendons in adult joints represent secondary invasions into the joints covered by reflected synovial membrane and are really external to the articular cavities. He also expressed the belief that the cells on the inner surface of the capsule merely flattened to form what he calls the epithelioid synovial membrane.

Bardeen<sup>7</sup> made the statement that the semilunar disks and the cruciate ligaments are differentiated directly from the blastema. He was unable to demonstrate any evidences of phylogenetic structures discarded during ontogeny.

Keith expressed the opinion that the menisci are remnants of the interchondral disks projecting into the gap between the articular surfaces. According to this author, the development of the femoral condyles toward the popliteal space isolates a posterior part of the capsule, which comes to lie within the joint and forms the cruciate ligaments. Occasionally the human knee communicates with the superior tibiofibular joint through the synovial diverticulum beneath the tendon of the popliteus muscle. The exclusion of the fibula takes place, according to Keith, about the eighth week of fetal life. He also made the statement that the articular cavity starts as five separate synovial compartments, which become continuous about the fourth month.

Keith said that all joints are formed by disappearance of cells from the interchondral disk, starting at the periphery, and that the perichondrium gives rise to the capsule. He insisted that the synovial membrane takes origin from the perichondrium and is cartilaginous in nature.

Bardeen stated that the menisci and the cruciate ligaments are differentiated directly from the blastema. He recorded the sequence of events as follows: menisci, capsule, cruciate ligaments, patella and finally ligamentum mucosum, all being derived from the blastema directly. He says a cavity is first seen between

4. Keith, A.: *Human Embryology and Morphology*, ed. 5, Baltimore, William Wood & Company, 1933.

5. Gray, H.: *Anatomy of the Human Body*, ed. 22, revised and reedited by Warren L. Lewis, Philadelphia, Lea & Febiger, 1930.

6. Arey, L. B.: *Developmental Anatomy*, Philadelphia, W. B. Saunders Company, 1925.

7. Bardeen, C. R.: *Human Embryology*, Philadelphia, J. B. Lippincott Company, 1910, vol. 1.

the patella and the femur at 30 mm. Lucien recorded the subsequent appearance of four other cavities. Limb buds may be noted toward the end of the third week. Between the fifth and the sixth week, definite outlines of the legs are recognizable. By the seventh week all the individual muscles of the adult except the lumbrical ones can be identified.

## MATERIAL AND METHOD

Fetuses of varying age groups were obtained from the surrounding hospitals. The embryologic collection of Harvard University was also utilized. In addition, surgical and postmortem specimens from the Children's Hospital were studied. They consisted of menisci and synovial membranes from about 50 knee joints varying in age from the eighth fetal month to the twelfth postnatal year.

The knee joints of the collection just mentioned were fixed in Bouin's solution for periods varying from three days to several weeks, as also were the menisci and the synovial membranes. They were then dehydrated with alcohols. The larger specimens were embedded in celloidin (a concentrated preparation of pyroxylin) and cleared in oil of Origanum after cutting. The smaller ones were cleared in cedar oil and xylene and embedded in paraffin. Serial sections of some of the joints were made in the coronal plane, while other joints were prepared in sagittal, transverse and oblique planes, respectively. The paraffin sections were 6 to 10 microns, while the celloidin ones were 15 to 20 microns, in thickness. From each group of five slides, two were stained with Mallory's hematoxylin and eosin, and one each with Mallory's phosphotungstic acid-hematoxylin, aniline blue and Foot's reticulum stain, and mounted in gum dammar, in routine fashion.

The embryologic material of the Harvard University collection had already been prepared in the form of serial section. The stains used in these were alum-cochineal and orange G, borax carmine and spirit blue, as well as carmine and iodine green.

Fifty joints representing age periods from the twentieth fetal day to three weeks after birth were studied, and 50 specimens of synovial membranes and menisci representing age periods up to the fifth year after birth were added.

## DATA

The youngest embryo examined was 20 days of age. At the age of 20 days the caudal limb buds are just appearing and are easily recognized both grossly and microscopically. They are composed of dense homogeneous blastemal tissue.

When the embryo has reached the age of 27 to 30 days, the hindlimb buds are larger but show no differentiation. Blood vessels are to be seen in the depth of the limb buds at 31 to 34 days, and nerve fibers are found growing into the bases of the buds. Definite condensation of the blastemal cells as anlagen of the skeletal structures is noted at 38 to 39 days. The anlage of the tibia and the fibula is a single sheet. The femur is well outlined in precartilaginous form at 47 to 51 days, and chondrification has begun. It is fairly well advanced in the center of the shaft, but less well developed toward the ends. Chondrification of the tibia is fairly well advanced but not as far as that of the femur. The anlagen of these two bones have always been separate. The tibia and the fibula are now recognized as having become separate from one another after having arisen as a single sheet of condensed blastema. The perichondrium is well developed and distinct. The interchondral scleroblastemal disk between the femur and the tibia is homogeneous and dense, with no evidence of a joint space. The femur and the tibia are at right angles to one another in the region of the future knee joint. The fibula does not enter into the formation of the knee joint by articulation with the femur except for the brief period of time during which the fibula and the tibia are one blastemal mass, before there is any evidence of a joint space. The foot plate is present at this stage.

8. Bardeen, C. R., and Lewis, W. H.: Development of the Limbs, Body Wall and Back in Man, *Am. J. Anat.* 1:1 (Nov. 7) 1901.

9. Bardeen, C. R.: Studies of the Development of the Human Skeleton. *Am. J. Anat.* 4:3 (May 25) 1905.

Between 52 and 55 days the process of chondrification is more advanced in the femur and the quadriceps muscle is recognizable. The region of the future knee joint is well demarcated and consists of the scleroblastemal disk between the femur and the tibia as described (fig. 1). The perichondrium still appears as condensed blastemal tissue with no further differentiation. The sciatic and tibial nerves are seen. Chondrification is more fully developed in the tibia and the fibula. There are no tibial spines. The condylar prominence of the distal end of the femur is present. The skeletal structures of the foot plate are seen in precartilaginous form.

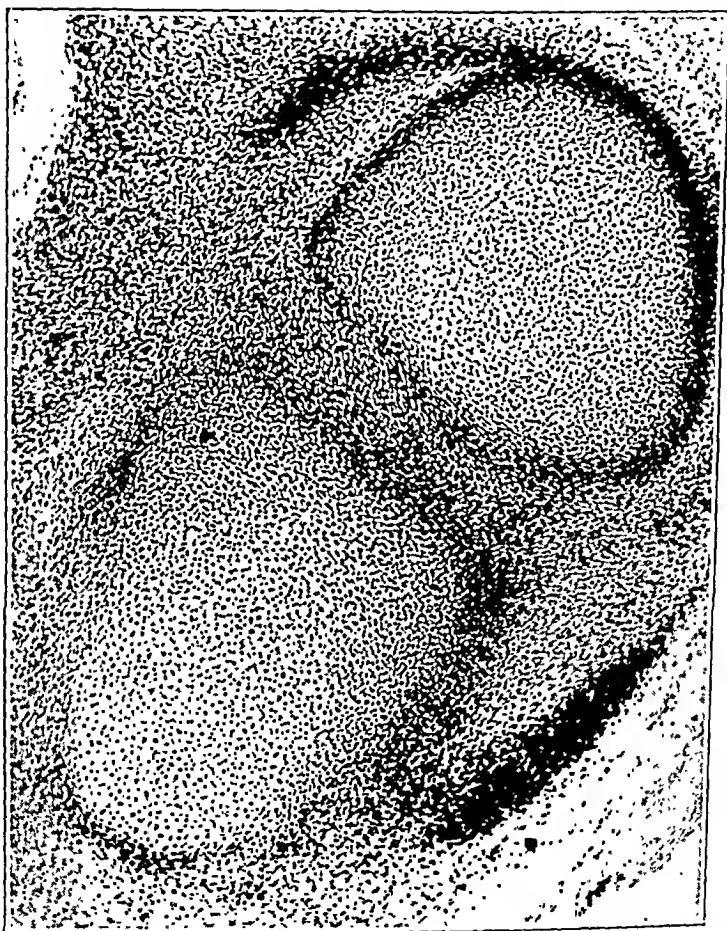


Fig. 1.—Photomicrograph of a transverse section of a knee joint at the fetal age of 52 to 55 days, showing a dense blastemal mass between the femur (upper bone) and the tibia (lower bone) with no evidence of a joint space. Alum-cochineal;  $\times 110$ .

At the age of 60 days the cartilage is more mature in appearance, with an increase in the amount of matrix. The interchondral disk has begun to show early and small degrees of decreased density and irregular loss of cellular substance anteriorly and posteriorly. These changes appear to be in the nature of a rapid and complete dissolution of the cells in the area without the finding of the different stages of disintegration. This loss of substance is the first sign of the formation of the cavity of the knee joint. Condensation of blastema for formation of the patella is noted. The central portion of the interchondral disk remains dense. The posterior curve of the femoral condyles is well developed.

At 8 to 9 weeks the femur, the tibia and the fibula consist of precartilage in the regions close to the knee joint but are composed of more mature cartilage away

from the joint. About all aspects of the bones is a condensation band of mesenchymal cells, forming a definite limiting membrane or perichondrium. In the region of the knee joint the space between the bones is filled by a mass of mesenchymal tissue or blastema which is somewhat less dense than that forming the perichondrium. The cells in the central portion of the joint area are compactly arranged while those at the periphery, although of like appearance, are less compact.

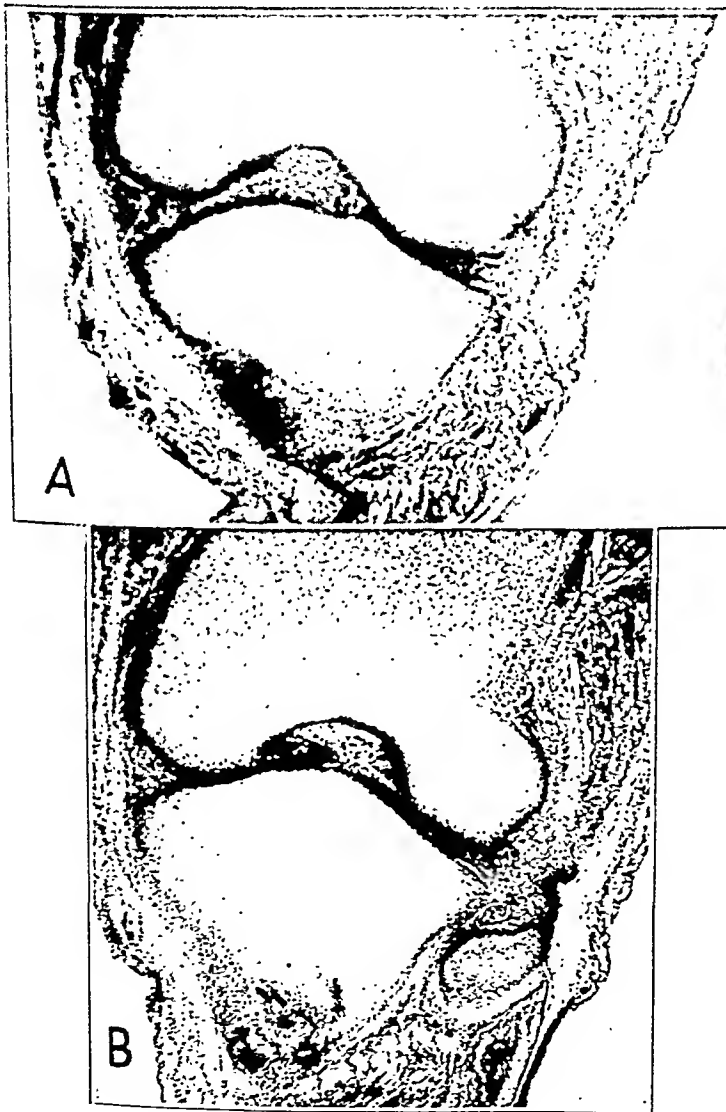


Fig. 2.—*A*, photomicrograph of a coronal section of a knee joint at the fetal age of 8 to 9 weeks, showing the earliest signs of formation of an articular cavity as slits in the dense mesenchymal mass between the femur (above) and the tibia (below). Hematoxylin and eosin;  $\times 28$ . *B*, photomicrograph of a coronal section of a knee joint at the fetal age of 8 to 9 weeks, showing early joint space as a slit in the mesenchymal tissue above the tibial condyle as well as minute cavities in the central portion of the interchondral disk. Note that the fibula (see to the right of the tibial condyle) does not articulate with the femur. Hematoxylin and eosin;  $\times 28$ .

Within the mass, toward the periphery, and on either side of the joint area, near the future articulating surfaces of the bones, are four slitlike openings (fig. 2*A*).

Over the proximal end of the tibia the two distal slits coalesce and the cavity extends across the entire joint area. In the region of the widest portion of the intercondylar notch, there is irregular vacuolation of the mesenchymal mass. There is no evidence of participation of the fibula in the knee joint, and the tibiofibular articulation is poorly demarcated (fig. 2*B*). The capsule is not yet present. The region of the menisci shows the dense arrangement of blastemal cells, but the form is only of broad masses with no actual separation of the parts into definite structures. Condensation of mesenchyma for development of the patella is recognized, and posterior to this is an incompletely developed cavity which does not communicate with the other cavities mentioned.

During the ninth to tenth weeks it is seen that the general contours of the tibia and the fibula are as in the adult except for indefinitely outlined tibial spines. The femoral condyles are better demarcated. The articular margins are composed of more mature cartilage than at eight weeks.

The joint space is quite well demarcated, even in the central portion, into four compartments, viz., one inferior to each femoral condyle, and one superior to each tibial tuberosity. Anteriorly these are separated by a mass of blastemal tissue in which are numerous small cavities of varying size with no definitely demarcated quadriceps pouch. The mass of blastema in the midline of the joint thus acts as a rather complete septum in the anteroposterior direction. The capsule is beginning to appear in the superior half of the joint and stands out prominently as a thin dense band of parallel young fibroblasts continuous with the perichondrium. The cruciate ligaments are easily recognizable as compact masses of wavy strands— young fibroblasts. Both cruciate ligaments are quite separate from each other and can be traced in all directions except at the anterior and the posterior portion of the joint. The menisci are well separated from the articular surfaces and consist of very dense crescentic masses of young fibroblasts with attachments to the capsule and the cruciate ligaments as noted in the adult. They are homogeneous throughout. The capsular tissue is less dense than the meniscal masses, and the cruciate ligaments are comparable to the capsule in this respect. In those areas where the menisci fuse with the capsular and cruciate ligaments and the superior surface of the tibia, the transition is an almost imperceptible one inasmuch as these structures are composed of tissue in essentially the same embryologic scale of differentiation. There is no well developed synovial membrane. No blood vessels are found except at the periphery of the joint, and as yet they have not penetrated any of the intra-articular structures. The cartilaginous patella has appeared.

At the age of 10 to 11 weeks the articular surfaces show little change from the picture seen in the embryo a week younger. The patella is easily recognized and consists of early cartilage. The articular cavity is somewhat more extensive in that the quadriceps pouch is better demarcated and the complete midline septum shows less prominently. The joint space is now rapidly approaching the shape of a single cavity of irregular outline with disappearance of a greater part of the aforementioned septum by coalescence of the small cavities previously mentioned (fig. 3). The cruciate ligaments and the menisci are now more mature in appearance but show no other changes. No blood vessels are seen in the menisci, but capillaries are noted in the blastema about the cruciate ligaments.

At the age of 12 weeks the cartilage of the distal end of the femur and the proximal end of the tibia is quite well developed and some bone is beginning to appear in the central portions of the shafts. The joint cavity consists of a large irregular space of essentially the same contour and relative size as seen in the

adult joint.<sup>10</sup> The menisci are well developed and crescentic in outline, as mentioned previously. They are attached at the periphery to the capsule, and a suggestion of coronary ligaments is now noted. It consists of a definite decrease in the density of the fibroblastic mass between the periphery of each meniscus and the capsule together with a differentiation in contour which outlines the border of the disk more sharply. In this region capillary blood vessels have penetrated from the capsule but do not appear to have progressed into the meniscus. Each meniscus presents a homogeneous cellular structure of fibroblasts (fig. 4). The tibial spines are recognizable. The cruciate ligaments are prominent and easily distinguished from one another by the direction of their parallel fibers. Surrounding these, the intercondylar notch contains a small amount of loosely arranged but quite well developed fibroblasts. The cavity is not lined by any specialized group or layer of cells. At this stage there appears to be no difference between

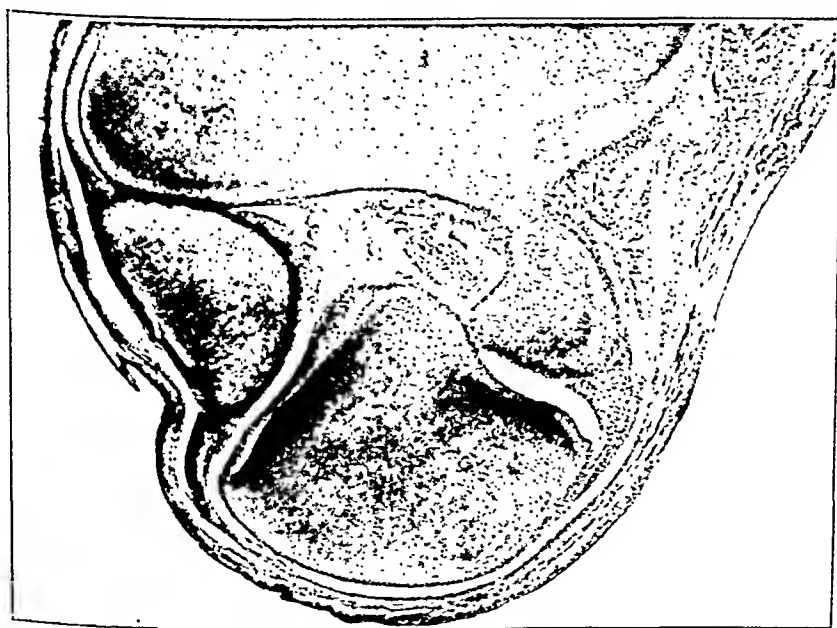


Fig. 3.—Photomicrograph of an oblique section of the knee joint at the fetal age of 10 weeks, showing a meniscus on the right between the femur (above) and the tibia (below), the patella (left) and the extent of the articular cavity. Hematoxylin and eosin;  $\times 28$ .

the cells covering the articular surfaces of the bones, those of the cruciate ligaments, those of the menisci, those of the coronary ligaments and those of the capsule except that the cells of the last two appear as somewhat more fully differentiated fibroblasts, while those of the menisci and the cruciate ligaments resemble less completely developed mesenchymal cells. The menisci are attached to the central portion of the tibia at their anterior and posterior ends, and are wedge shaped in cross section.

The picture at 12½ weeks shows the articular cartilage somewhat more mature, but it continues to be covered by the cell layer previously described. The cells of the menisci, periosteum, capsule, cruciate ligaments and coronary ligaments appear to be better differentiated (fig. 5A). Blood vessels are seen

10. Flint, J. M.: Notes on the Form of the Cavity of the Knee Joint, Bull. Johns Hopkins Hosp. 15:163 (Oct.) 1904.



in the loose tissue surrounding the cruciate ligaments and in some areas appear to be entering the menisci from the coronary ligaments. The ligament of Wrisberg and the ligamentum transversum have not been recognized. The ligamentum mucosum and the alar ligaments have as yet shown no definite outline.

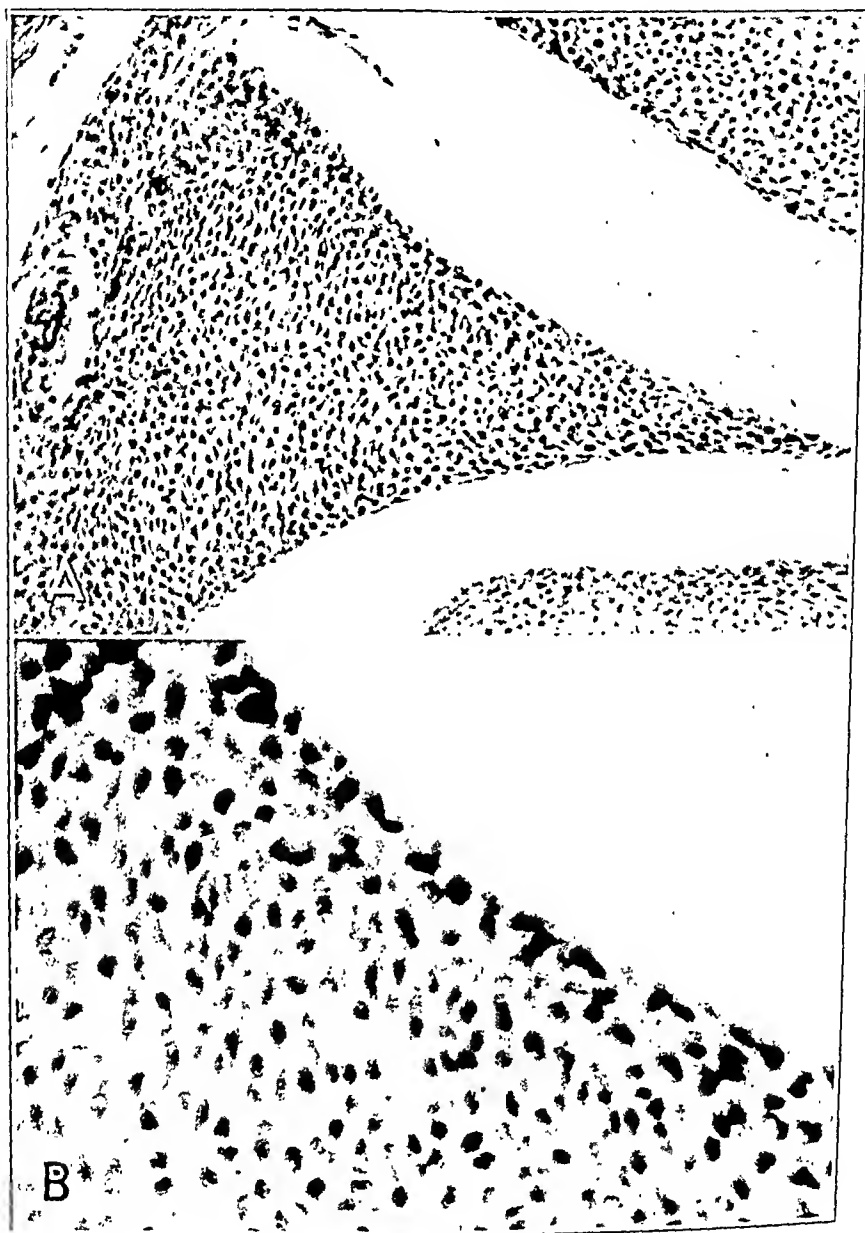


Fig. 4.—*A*, photomicrograph of a meniscus at the fetal age of 12 weeks. No cartilage matrix is present, and the synovial membrane has not made its appearance. Hematoxylin and eosin;  $\times 200$ . *B*, photomicrograph at higher magnification of a portion of the meniscus shown in *A*. There is uniformity of cellular structure, with no evidence of a synovial layer. Hematoxylin and eosin;  $\times 560$ .

In the embryo of 13 weeks little change as far as differentiation is concerned can be seen. The menisci appear to contain collagenous matrix, and there is abundant reticulum. There is no synovial lining over the articular surfaces. The

blood vessels are now seen in the periphery of the menisci and in the connective tissue about the cruciate ligaments.

At the age of approximately  $13\frac{1}{2}$  weeks, the cartilage of the joint shows further progression toward maturity and the same layer of flattened, elongated cells persists



Fig. 5.—*A*, photomicrograph of a coronal section of a knee joint at the fetal age of  $12\frac{1}{2}$  weeks, showing well developed menisci and the extent of the articular cavity. Hematoxylin and eosin;  $\times 19$ . *B*, photomicrograph of an oblique section of a knee joint at the fetal age of  $13\frac{1}{2}$  weeks, showing the contour of the joint space, the menisci and prominent cruciate ligaments (center). Aniline blue;  $\times 20$ .

over the articular surfaces. There is more collagenous matrix, and the reticulum in the capsule and menisci as well as in the cruciate and coronary ligaments is less. There is a hardly perceptible union of coronary ligaments and

meniscuses. The latter are of the same distribution and configuration as the adult disk. The cells forming the meniscuses show an increasing tendency for their fibers to be arranged as straight and slightly wavy collagen bundles. The cruciate ligaments are better separated from the meniscuses at the anterior and posterior ends of the latter. They can now be recognized as separate entities because of



Fig. 6.—Photomicrograph of a coronal section of a knee joint at the fetal age of 15 to 16 weeks, showing the meniscuses and the cruciate ligaments, which, together with the joint space, show little change from the status seen in figure 5*B* other than increase in size. Hematoxylin and eosin;  $\times 16.5$ .



Fig. 7.—Photomicrograph of a portion of a meniscus at the fetal age of 20½ weeks. The cellular detail is well shown (fibroblasts), and the definition of a synovial layer is striking as a special arrangement of the surface fibroblasts. Hematoxylin and eosin;  $\times 350$ .

the fact that the point of union is marked by less densely compacted cells (fig. 5*B*). The ligamentum mucosum and the alar ligaments are composed of well developed

fibroblasts with a small amount of collagen. They are moderately vascular, the vessels being chiefly capillaries and small vessels with poorly developed walls. No definite synovial membrane is recognized. The mesenchymal tissue about the cruciate ligaments is smaller in amount, loose and edematous and shows areas of degeneration.

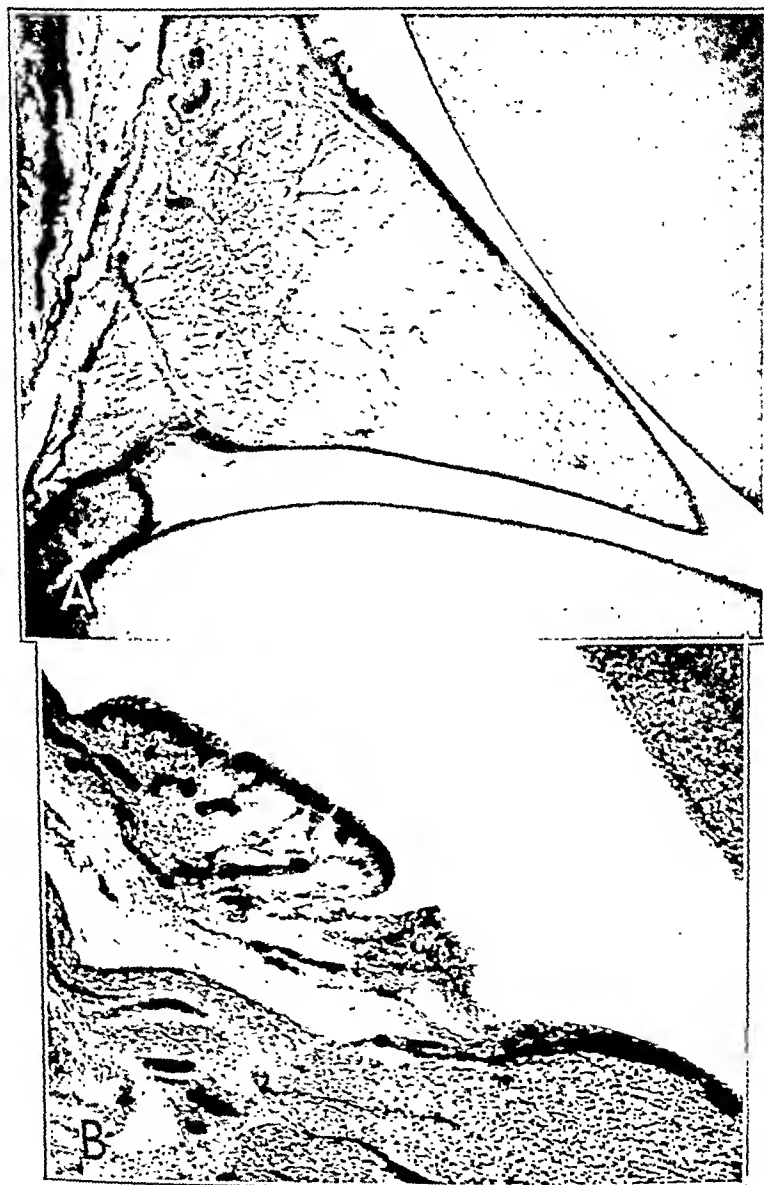


Fig. 8.—*A*, photomicrograph of a sagittal section of a coronary ligament and a meniscus at the postnatal age of 3 weeks. A dense synovial layer is seen covering the entire free surface of the meniscus. Note the small blood vessels in the coronary ligament and in the outer two thirds of the meniscus, with a relatively avascular central region of the latter structure. Hematoxylin and eosin;  $\times 22$ . *B*, photomicrograph of a sagittal section of a coronary ligament and a meniscus with the adjacent joint surface at the postnatal age of 3 weeks. Note the absence of a synovial covering over the articular cartilage at the right upper corner. Hematoxylin and eosin;  $\times 60$ .

During the following two to three weeks the changes are chiefly those of increased growth and more complete differentiation of individual cells (fig. 6). The articular surfaces of the bones are covered by a thin layer of flattened cells, and beneath this normal hyaline cartilage is easily recognized. Blood vessels can be seen in the outer portions of the menisci. The connective tissue about the cruciate ligaments is more loosely arranged, less in amount and more vascular. The menisci are very compact and contain increasing amounts of collagen, but no cartilage matrix.

At the age of 18 weeks growth has become more and more rapid and the process of differentiation more complete. The menisci show blood vessels extending well into them, even to their tips, so that they are highly vascular in some places. The cruciate ligaments stand almost alone, and a few vascular



Fig. 9.—Photomicrograph of the free border of a meniscus at the age of  $5\frac{1}{2}$  years, showing the presence of a synovial membrane over the vascular external portion on the left and abrupt disappearance of the membrane over the avascular weight-bearing area. Hematoxylin and eosin;  $\times 150$ .

elements are noted within them. A definite synovial lining is not seen, but in some areas on the surfaces of the menisci the cells appear to be undergoing rearrangement. This consists merely of a more dense grouping of the constituent cellular elements involving those closest to the free surfaces for a depth of four or five cells.

During the following week the chief changes in addition to growth are the increase in vascularity of the cruciate and coronary ligaments and the appearance of definite fat cells in the mass of connective tissue inferior to the patella, so that now a definite infrapatellar fat pad becomes a reality. Previously there has been only a mass of loosely arranged fibrous tissue. The synovial membrane is not as yet definite.

When the embryo has reached 20½ weeks, the femoral condyles are quite prominent and the intercondylar notch proportionately deep. Each articulating surface presents, parallel to the surface, a thin layer of elongated cells, between which one finds little matrix. It now resembles very closely that in the adult. Reticulum is no longer present in this region. Along the free borders of each meniscus the cells are somewhat more flattened and form a distinct compact layer. Some of the surface cells project into the cavity. This layer, although composed of the same elements as the bulk of the meniscus, is different in the arrangement of its cells. It is interpreted as being the first definite evidence of the formation of a more specialized layer lining the joint, and may be called the synovial membrane (fig. 7). It is not uniform and in some areas appears to extend over the entire meniscus as far as the latter's attachment to the capsular and coronary ligaments and for a short distance over the joint aspects of these structures. No synovial membrane is seen in other portions of the joint except possibly over portions of the ligamentum mucosum and alar ligaments. The regions immediately beneath the synovial membrane are very vascular.

At 29 to 30 weeks there is little increase in the amount of adipose tissue in the future infrapatellar fat pad. There has been great increase in growth of all the structures with little modification of form. The articular surfaces are more mature and are now composed of hyaline cartilage to their ends, except for a few flattened elongated cells. The synovial membrane appears to line the entire joint space except over the ends of the bones. Synovial villi are beginning to make their appearance.

At birth the changes from the foregoing picture are of growth only. The menisci are covered by synovial membrane on all aspects except at the point of attachment to the coronary ligaments and the capsule (fig. 8). They are quite vascular except at their tips.

During the following two to three years the alterations within the knee joints are primarily those of growth with one striking exception, viz., the menisci become more and more avascular and the amount of collagen increases rapidly. The final result is that they consist of masses of dense collagenous tissue, the inner two thirds of which is entirely without blood vessels. Equally striking is the fact that the synovial membrane disappears from the free borders in those areas which bear weight (fig. 9). At no time during childhood was any suggestion of cartilage matrix noted in the menisci.

#### COMMENT

In the microscopic development of the human knee joint it is difficult to recognize any but a few definite manifestations of phylogenetic phenomena.<sup>7</sup> However, they can be recognized readily in the infrequent congenital anomalies seen at operations, at postmortem examinations and in dissecting rooms.<sup>11</sup> Discoid and ring-shaped menisci are not too infrequently encountered, and their origin is explained by those interested in comparative anatomy.<sup>12</sup> The same applies to various types of division of the articular cavity and types of meniscal attachment.<sup>13</sup>

It is important to appreciate the fact that the menisci are well developed long before there is any suggestion of a synovial lining in the joint, especially

11. Chandler, F. A.: Congenital Abnormalities of the External Semilunar Cartilage, *S. Clin. North America* 17:331-334 (April) 1937. Ellis, V. H.: Congenital Abnormality of External Semilunar Cartilage, *Lancet* 1:1359 (June 25) 1932.

12. Finder, J. G.: Discoid External Semilunar Cartilage, *J. Bone & Joint Surg.* 16:804 (Oct.) 1934. Jaffe, H. L.: Comparative Anatomy of Semilunar Cartilages of the Knees: Normal Presence of Bone in Menisci of Some Animals, *Arch. Path.* 15:599 (April) 1933.

13. Herzmark, M. H.: Evolution of the Knee Joint, *J. Bone & Joint Surg.* 20:1 (Jan.) 1938.

when one attempts to explain the genesis of meniscal cysts on a developmental basis.<sup>14</sup> The fact that the synovial membrane is first seen at approximately the time fetal movements are usually recognized by the mother is certainly interesting. Also it seems that this covering disappears from those portions of the menisci that are exposed to weight bearing at the period when the child is beginning to bear weight and use his knee joints really well.<sup>15</sup>

Nothing which could contribute to the information on the origin of synovial fluid was recognized in this study with one exception. It is quite definite that the synovial membrane is entirely derived from connective tissue, by rearrangement of cells rather than by special differentiation.

The menisci which are so commonly termed semilunar cartilages are in childhood, at least, composed of collagenous tissue, and one may well feel that the term "menisci" is preferable.

The intra-articular structures, which are derived from a common source, appear to arise directly in the same relative position in which they are found in the fully developed joint. Accordingly it is difficult to accept the suggestion that the menisci and the cruciate ligaments are secondary invasions into the joints with reflected synovial membrane to cover them. Furthermore, the synovial membrane appears to result only from a rearrangement of fibrous tissue cells on the inner surface of the capsule and over the free borders of the menisci; it has the same origin as the structures it covers and does not present an appearance which would suggest an epithelial or an endothelial nature.

Keith's idea that the cruciate ligaments arise from inclusion of a portion of the posterior capsule within the joint does not seem to be borne out by my observations that the curve of the condyles changes little if any after the appearance of the capsule. The cruciate ligaments can be seen to arise directly by condensation and differentiation of the blastemal tissue of the intercondylar disk as early as 9 to 10 weeks, at which time the capsule is little in evidence.

The perichondrium is well differentiated before the appearance of the synovial membrane. Although both have a common source in the undifferentiated blastema of the limb bud, it does not seem reasonable to assume that the perichondrium gives rise to the synovial lining of the joint as Keith suggests.

I was able to recognize cruciate ligaments prior to the appearance of the capsule, contrary to the observations of Bardeen, but am in agreement with his statement that the menisci and the cruciate ligaments are differentiated directly from the blastema.

#### SUMMARY

The development of the knee joint is traced by means of serial sections from the third week of fetal life to birth, and the menisci are studied to the age of 12 years. Particular emphasis has been placed on the embryologic origin of the intra-articular structures and the chronologic relationship between the menisci and the synovial membrane. Topographic rearrangements of the synovial membrane in early childhood are recorded.

A review of some of the literature on the knee joint in the field of comparative anatomy, as well as a review of the more significant available literature in that of embryology, has been included.

14. King, E. S. J.: The Formation of Ganglia and Cysts of the Menisci of the Knee: Observations on the Golgi Apparatus, *Surg., Gynec. & Obst.* 70:150 (Feb.) 1940.

15. MacConaill, M. A.: The Function of Intra-Articular Cartilages, *J. Anat.* 66:210 (Jan.) 1932.

## CONCLUSIONS

1. The articular cavity of the knee joint develops by disappearance of cells from the substance of the dense blastemal interchondral disk between the tibia and the femur, with coalescence of several primary spaces.

2. The menisci and the intra-articular ligaments, as well as the capsule, are differentiated directly from the blastema which remains after the disappearance of cells resulting in the formation of the joint space.

3. The synovial membrane makes its appearance by rearrangement of cells over the free borders of the menisci and the inner surface of the capsule after these structures have been well differentiated.

4. At no time does the synovial membrane cover the articular surfaces of the bones.

5. The synovial membrane does not consist of endothelial cells.

6. The menisci are fully developed several weeks before the appearance of the synovial membrane.

7. Limb buds are seen during the third week of fetal life.

8. The time of appearance of various structures of the knee joint is as follows: joint space, eighth week, complete at the twelfth week; menisci, ninth to tenth week; capsule, ninth to tenth week; cruciate ligaments, ninth to tenth week; cartilaginous patella, tenth week; coronary ligaments, twelfth to thirteenth week; synovial membrane, eighteenth to twentieth week; infrapatellar fat pad, nineteenth week; synovial villi, twenty-ninth to thirtieth week.

9. After birth the inner two thirds of the menisci becomes increasingly avascular, and at about  $2\frac{1}{2}$  years of age the synovial membrane has completely disappeared from these weight-bearing areas of the menisci.

10. During childhood the menisci contain no cartilage matrix.

11. Few definite evidences of phylogenetic phenomena are noted in serial sections of the knee joints.

12. The term "menisci" is to be preferred to "semilunar cartilages" when referring to the intra-articular disks of the knee joint.

## ADDENDA

The data and criteria for determination of fetal age were based on foot length and crown-rump length as well as crown-heel length of the fetus.

Guidance, criticism and advice in this work were given by Dr. Frank R. Ober, John Ball and Buckminster Brown professor of orthopedic surgery at Harvard Medical School; Dr. William T. Green, assistant professor of orthopedic surgery; Dr. Sidney Farber, assistant professor of pathology, and Dr. Granville A. Bennett, assistant professor of pathology. Permission to use the embryologic collection of Harvard Medical School was given by Dr. J. Lewis Bremer, Hersey professor of anatomy. Miss Mary McNally prepared serial sections of specimens; Mr. Charles Miller made the photomicrographs, and Miss Helen Purtle, of the department of pathology of the Children's Hospital, aided in the revision of the manuscript.



# FRACTURE OF THE NECK OF THE ASTRAGALUS

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In the past quarter century, spanning the years 1919 to 1943, fracture of the neck of the astragalus has received but scant attention. The few reported end results have been discouraging. A search of the literature over this period reveals not more than seventy-five papers dealing with this injury. These contributions, for the most part, are in the foreign literature.

Most of these reports record isolated instances of fracture of the astragalar neck because of its rarity. The commonly employed therapy has been total or partial astragalectomy. This form of treatment in the case of an adult is an admission of inadequacy surpassed only by amputation.

In the English literature of these same years there have been twenty-one treatises on fracture involving the neck of the astragalus. Seventeen reports have been from the United States; four have been from Great Britain. Again, the majority of these papers have value only as tabulations of individual cases, and astragalectomy, total or partial, has been the usual treatment. Only nine works in the English language deserve special consideration.

Sneed<sup>1</sup> reported the case of a patient with total dislocation of the astragalus who refused to submit to astragalectomy. Reduction was accomplished only after complete excision and replacement of the astragalus. The articular cartilage was not eradicated from either the tibial or the calcaneal surface of the bone. It is stated that four years after this injury the patient had a satisfactory functional result and a painless foot, although dorsiflexion and plantar flexion of the ankle joint were moderately limited and motion in the subastragalar joint was markedly restricted.

Sneed also carried out a series of injections on amputated legs and from these experiments inferred that the astragalus is supplied with blood not by one main nutrient artery but by several small arteries. He concluded that even though the vascular supply of the astragalus is interrupted, replacement of the bone offers hope of good function. It is interesting that his one photograph demonstrating blood vessels in the astragalus by injection shows them to be present only in the neck and to originate on the superior surface.

Graham and Faulkner<sup>2</sup> reviewed the case records of 10 patients who were seen late and who were treated by total astragalectomy. Although they granted the severe disability resulting from astragalectomy, they held this procedure to be the one of choice for patients coming under observation late or for patients coming under observation early with severe comminution of the astragalar body. For patients seen reasonably early without severe comminution of the astragalus, they advocated open replacement as offering less disablement in the future.

Phemister<sup>3</sup> at a meeting of the American Orthopedic Association in 1932 presented an experimental study, "Transplantation of the Astragalus," which has

1. Sneed, W. L.: Astragalus: Case of Dislocation, Excision, and Replacement; an Attempt to Demonstrate Circulation in This Bone, *J. Bone & Joint Surg.* 7:384-399 (April) 1925.

2. Graham, W. T., and Faulkner, D. M.: Fractures of the Astragalus: Ten Cases Treated by Astragalectomy, *Ann. Surg.* 89:435-438 (March) 1929.

3. Phemister, D. P.: Transplantation of the Astragalus, to be published.

a direct bearing on the problem of treatment of fracture of the neck of the astragalus. He showed in animals that the enucleated astragalus when replaced constantly underwent aseptic necrosis. However, when the articular cartilage was removed from the bone, revascularization was tremendously accelerated. He concluded that the articular cartilage acted as a barrier to the ingrowth of new blood vessels.

In 1940 Phemister<sup>4</sup> reported 2 cases of aseptic necrosis of the astragalus after fracture, in 1 of which there was no displacement of the fragments, and called attention to the effect of degeneration of the underlying bone on the articular cartilage of the astragalus. In this article he presented excellent pathologic studies.

Gibson and Inkster<sup>5</sup> contributed an excellent consideration of the mechanogenesis of this fracture. They attributed some vascular supply to small arteries entering the astragalus through the attachments of the deltoid ligaments. Certain criteria for treatment were outlined. In their opinion a complete posterior dislocation of the body through a buttonhole between the flexor tendons completely severed the body of the astragalus from its vascular connections. They felt that in this circumstance simple replacement leads to necrosis of the body and advised panastragalar arthrodesis. A perusal of the roentgenograms reproduced in their paper reveals aseptic necrosis of the astragalus even in their patients who did not have such severe dislocation. They condemned partial astragalectomy as producing a heel walker.

Conwell and Alldredge<sup>6</sup> reported on a patient who suffered a compound fracture-dislocation of the astragalus. The fragments were replaced without erasing the cartilage. The result after eleven months is shown. Although severe deformation and considerable sclerosis of the astragalus resulted, the authors maintained that this procedure is superior to astragalectomy and subscribed to the statement of Sneed that revascularization of the bone may occur.

Miller and Baker<sup>7</sup> in reporting a series of cases of fracture of the astragalus advised against astragalectomy and recommended that triple arthrodesis be performed early if accurate reduction is impossible. Nineteen of his patients were followed long enough to be considered as showing end results. Of these 19 patients, 15, or 79 per cent, had pain, deformity or limp, or all three, and 1 had an elective amputation. They quoted Sneed's work of 1925 in stating that the astragalus has no main nutrient artery.

Boyd and Knight<sup>8</sup> called attention to the poor results obtained in treating fractures of this type and advised open reduction if there is any displacement and stated that severe displacement may require subastragalar fusion. They condemned astragalectomy.

Schrock, Johnson and Waters Jr.<sup>9</sup> called attention to the constancy of sclerosis of the body of the astragalus and of traumatic arthritis of the tibiocalcaneal joint. Later, however, they attributed this to crushing trauma of the dome of the

4. Phemister, D. B.: Changes in Bones and Joints Resulting from Interruption of Circulation, *Arch. Surg.* **41**:436-472 (Aug.) 1940.

5. Gibson, A., and Inkster, R. G.: Fractures of the Neck of the Astragalus, *Canad. M. A. J.* **31**:357-362 (Oct.) 1934.

6. Conwell, H. E., and Alldredge, R. H.: Complete Compound Comminuted Fracture-Dislocation of Astragalus, *Surgery* **1**:222-227 (Feb.) 1937.

7. Miller, O. L., and Baker, L. D.: Fractures of the Astragalus, *South. M. J.* **32**:125-136 (Feb.) 1939.

8. Boyd, H. D., and Knight, R. F.: Fractures of the Astragalus, *South. M. J.* **35**:160-167 (Feb.) 1942.

9. Schrock, R. D.; Johnson, H. F., and Waters, C. H., Jr.: Fracture and Fracture-Dislocations of the Astragalus (Talus), *J. Bone & Joint Surg.* **24**:560-569 (July) 1942.

astragalus with infractions of the articular cartilage rather than to disturbance of circulation. They advised against astragalectomy and proposed a tibial-astragalar-calcaneal arthrodesis, using, if necessary, fragments of a comminuted astragalus. They reported 6 cases of fracture of the neck of the astragalus.

Modern textbooks of orthopedic surgery and of the treatment of fractures also offer a variety of opinions concerning the treatment of fracture of the type under discussion.

Böhler<sup>10</sup> presented fracture of the neck of the astragalus as a simple mechanical problem, stating that as a rule it is reduced by traction but that occasionally it requires open reduction, which results in good function after eight weeks' immobilization. He advised against astragalectomy but gave no consideration to any vascular disturbance and disregarded the physiology of repair.

Speed<sup>11</sup> recommended simple immobilization in cases in which there is no displacement or in which reduction can be effected. For cases in which reduction is impossible he advised removal of the displaced fragment (partial astragalectomy). He stated that most of the fractures of this type eventually come to astragalectomy and stressed the frequency of infection after open reduction.

Magnuson<sup>12</sup> stated that in cases of fracture of the neck of the astragalus with displacement there is always some permanent disability. He said, "Because of complete loss of blood supply the fracture does not heal kindly and consequently the fragment may form a foreign body in the joint." For fracture with displacement he advocated arthrodesis of the ankle joint.

Destot<sup>13</sup> stressed the mechanical difficulties of both accurate open and closed reduction and emphasized the importance of accurate replacement. He advised against partial astragalectomy and held that total astragalectomy should be reserved for those cases in which the body of the astragalus is damaged or those in which open reduction is impossible. Closed reduction is only occasionally successful, he stated. No illustrations of the blood supply are offered, but Ollier is quoted as saying that the astragalus is a poorly nourished bone and that the lack of nourishment accounts for the frequent localization of tuberculosis in this region.

Wilson<sup>14</sup> called attention to the fact that the nutrition of the astragalar body is cut off if there is displacement. On the basis of results in 5 patients, 4 of whom were treated by total astragalectomy and 1 of whom was treated by replacement, he had become a protagonist of astragalectomy and advised against replacement. Fifty per cent of the patients subjected to astragalectomy were reported as having a good result, and in the 1 patient in whom replacement was carried out the end result was a failure.

Scudder<sup>15</sup> in a brief paragraph dismissed fracture of the astragalus with the statement that after two to three months of immobilization of the foot the patient may walk without support but may have some pain for four to six weeks after the injury. The illustrations in the eleventh edition of his work are taken from Cabot and Binney and clearly show circulatory changes in the body of the astragalus.

10. Böhler, L.: *Treatment of Fractures*, ed. 4, translated from the fourth German edition by E. W. H. Groves, Baltimore, William Wood & Company, 1941.

11. Speed, K.: *Fractures and Dislocations*, Philadelphia, Lea & Febiger, 1942.

12. Magnuson, P. B.: *Fractures*, ed. 3, Philadelphia, J. B. Lippincott Company, 1939.

13. Destot, E.: *Traumatismes du pied et rayone X*, ed. 2, Paris, Masson & Cie, 1937.

14. Wilson, P. D.: *Management of Fractures and Dislocations*, Philadelphia, J. P. Lippincott Company, 1938.

15. Scudder, C. L.: *The Treatment of Fractures*, ed. 11, Philadelphia, W. B. Saunders Company, 1938.

Key and Conwell<sup>16</sup> held that astragalectomy is indicated only in the presence of sepsis. For severe displacement they advised panastragalar arthrodesis to prevent aseptic necrosis of the proximal fragment. Their illustrations clearly demonstrate the lack of demineralization posterior to the fracture line.

Watson-Jones<sup>17</sup> offered sketches of the blood supply of the astragalus showing vessels entering all ligamentous attachments in great adequacy and called attention to the seriousness of avascular necrosis as a disabling factor. He stated, however, that the blood supply of the astragalus is sufficient to prevent avascular necrosis

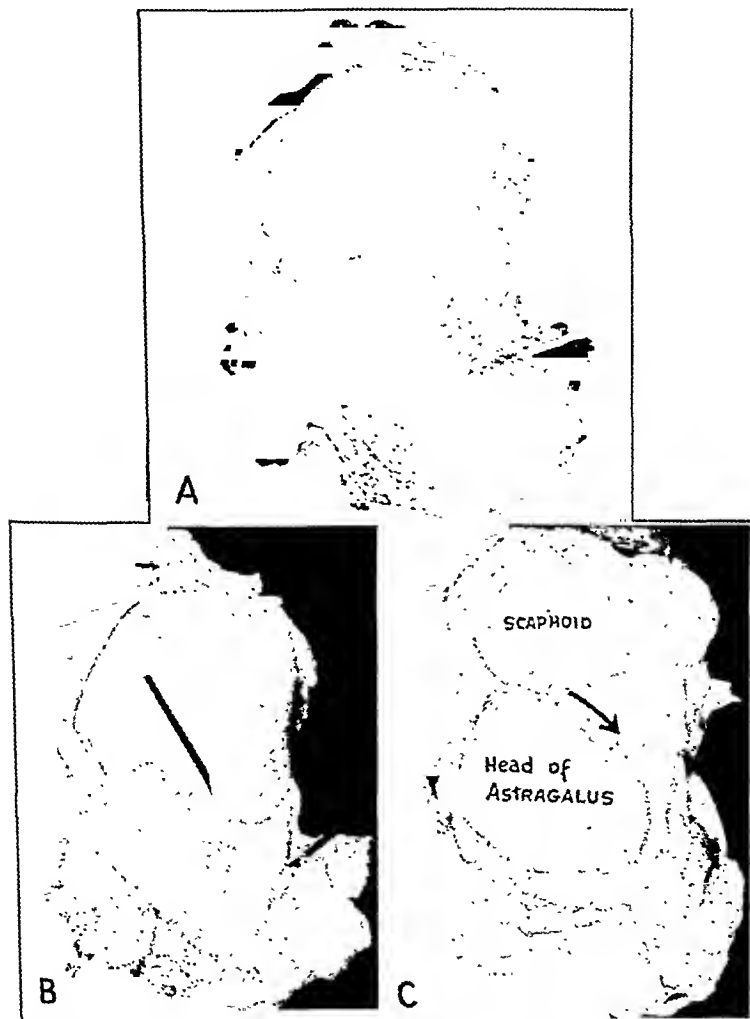


Fig. 1.—*A*, astragalus with the superior astragaloscaphoid ligament attached to its neck and a pointer in its artery. *B*, astragalus with the superior astragaloscaphoid ligament reflected forward and arrows pointing to vessels going into the portion of the neck not covered by cartilage between the body and the head. *C*, astragalus, scaphoid and attached superior astragaloscaphoid ligament. The scaphoid is lifted up, with the head of the astragalus facing. Vessels in the superior astragaloscaphoid ligament are going into the neck near the body.

16. Key, J. A., and Conwell, H. E.: *Fractures, Dislocations, and Sprains*, ed. 3, St. Louis, C. V. Mosby Company, 1942.

17. Watson-Jones, R.: *Fractures and Other Bone and Joint Injuries*, Baltimore, Williams & Wilkins Company, 1940.

unless backward dislocation of the body occurs. This is not borne out by clinical experience, and it is believed he attributed too ample a circulation to the astragalus.

The purpose of the present paper is to present (1) the intrinsic circulation of the astragalus as revealed by injection, (2) the end results in 17 patients who suffered fracture of the neck of the astragalus and (3) some principles of treatment based on a study of the circulation of blood in the bone and of the clinical course of fracture of the astragalar neck.

#### INTRINSIC CIRCULATION OF THE ASTRAGALUS AS REVEALED BY INJECTION

To demonstrate the arterial ramifications in the astragalus, freshly amputated feet were used. The vascular system of each amputated specimen was first washed

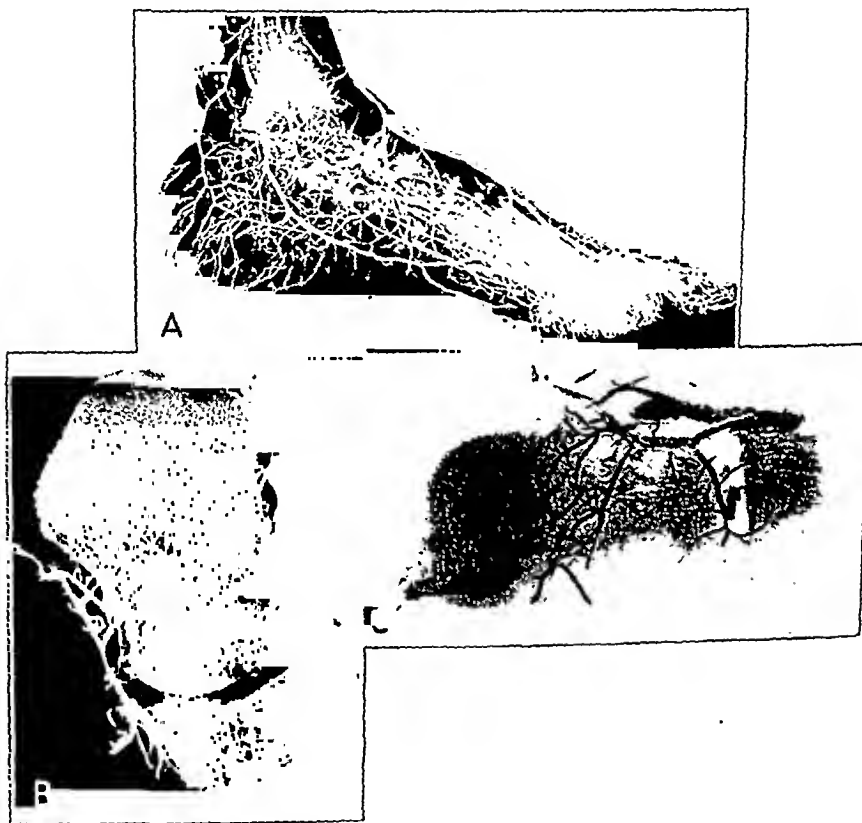


Fig. 2.—Roentgenograms: *A*, foot with the soft tissues intact, after metallic mercury had been injected into the vascular system. A branch of the anterior tibial artery goes to the astragalar neck. The posterior tibial artery passes by the astragalus. The vascular network even in the soft tissues in the region of the astragalus is sparse compared with the remaining vascular bed. *B*, anteroposterior view of the astragalus and the scaphoid with all ligaments attached. The vessels in the superior astragaloscaphoid ligament with their ramifications to the neck stand out plainly. *C*, lateral view of the same specimen. Note the lack of vascularity posterior to the neck.

by perfusing with tap water for six to eight hours. The arterial trunks, the anterior tibial artery and the posterior tibial artery were then injected with a radiopaque medium under pressure. In some instances metallic mercury was used. In others a suspension of yellow oxide of lead (lead monoxide N. F.) in olive oil was the substance injected. The venous side was ligated before the injections were made.

After the injections had been made, roentgenograms were obtained of (1) the entire foot, (2) the astragalus and the scaphoid with all attached ligaments but without other soft tissue and (3) the isolated astragalus, scraped clean of all ligaments.

Seven feet were used. They were all free of arterial disease and had been amputated for morbid conditions higher in the extremity or distal to the ankle, such as osteogenic sarcoma of the femur, intractable sepsis at the knee and complete traumatic amputation. In 4 of the specimens after the astragalus had been cleanly denuded of all ligaments the isolated bone failed to show evidence of the injected

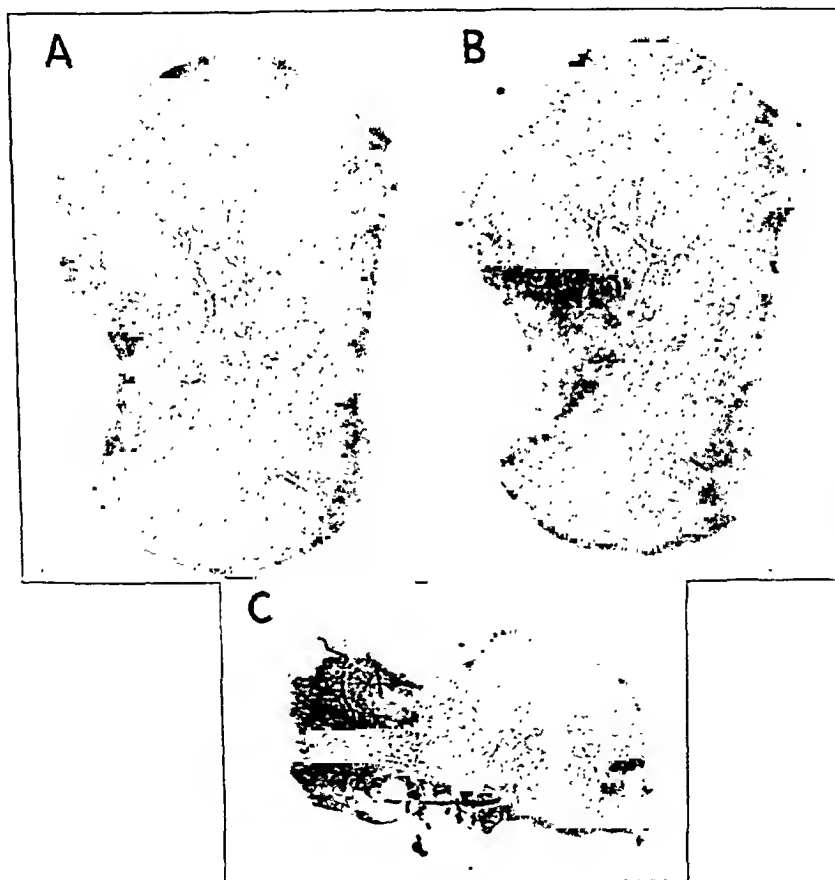


Fig. 3.—Roentgenograms: *A*, anteroposterior view of the astragalus scraped clean of all ligaments. The injected material in the bone is largely in the neck region. The body shows no evidence of blood vessels in the interior. *B*, posterior-anterior view of the same specimen. *C*, lateral view of the same specimen. Note the absence of injected material in the posterior third and the preponderance of vessels in the neck.

material within its substance despite the fact that the arterial tree of the overlying soft tissues was completely outlined. This suggests that the arteries entering the astragalus are of small caliber.

The injected arteries suggest that the entire vascular supply of the astragalus is derived from branches of the anterior tibial artery. There is evidence also that the artery, which eventually breaks up into several nutrient arteries, is carried in the dense astragaloscaphoid ligament (*B N A. ligamentum talonaviculare dorsale*)

which extends as a broad band from the dorsal surface of the neck of the astragalus to the dorsal periphery of the scaphoid. In this ligament the artery divides into several (two to four) smaller arteries which perforate the superomedial aspect of the neck of the astragalus, where foramina are clearly present.

No evidence of arteries perforating from either the posterior or the anterior calcaneoastragalar ligament or from the internal calcaneoastragalar ligaments in the subastragalar joint was apparent. In no instance was it possible to demonstrate arteries throughout the body of the astragalus.

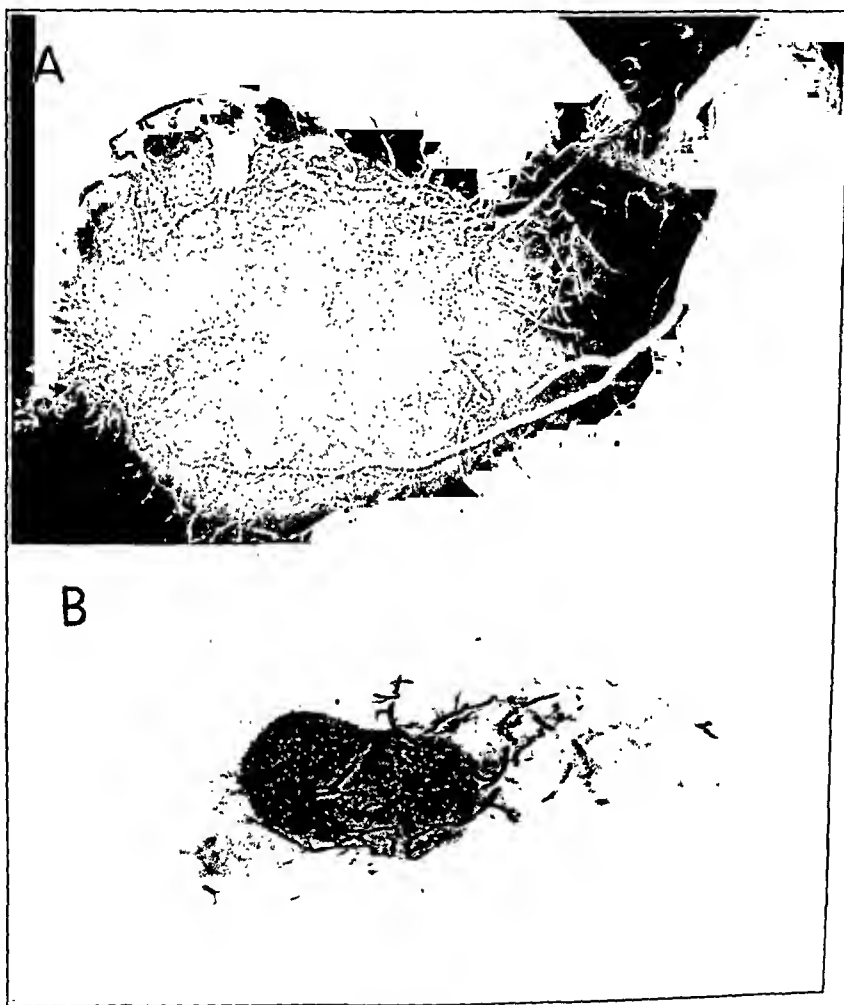


Fig. 4.—Roentgenograms: *A*, foot of a 4 month old infant in which the vessels have been injected with lead monoxide in olive oil. The posterior tibial artery gives off no branches to the astragalus. All vessels going to this area come from the dorsum of the foot. The foot was amputated for fibrosarcoma. *B*, astragalus, scaphoid and all ligaments. The scaphoid does not show because of the lack of an ossification center at this age, and only the nucleus of the astragalus is clear. Note the vessels in the superior astragaloscaphoid ligament.

#### SURVEY OF PATIENTS AND THEIR TREATMENT

Seventeen patients who suffered a fracture of the neck of the astragalus were examined clinically and studied by roentgenograms to determine the end results of various treatments and the relation of the original displacement of the fractured

fragments to the outcome. The shortest period that elapsed after the injury in any case was one and one-half years and the longest was eleven years.

Of these 17 patients, all but 3 (82 per cent) were under 40 years of age, in the active, vigorous period of life. Three were children. In 5 patients the fracture was subjected to open reduction. In all of these the body of the astragalus was completely removed and replaced in its entirety, with all articular cartilage intact. Six patients were treated by closed manipulation and immobilization of the extremity. Simple immobilization of the foot and leg in plaster was all that was necessary for 5 patients, due to the fact that there was no displacement of the fragments. Astragalectomy was done on 1 patient.

#### RESULTS

Only 4 of the 17 patients (23 per cent) were free of pain, had no restriction of motion in the ankle or the subastragalar joint and could carry on normal activity. These 4 were all patients who had sustained incomplete fracture of the

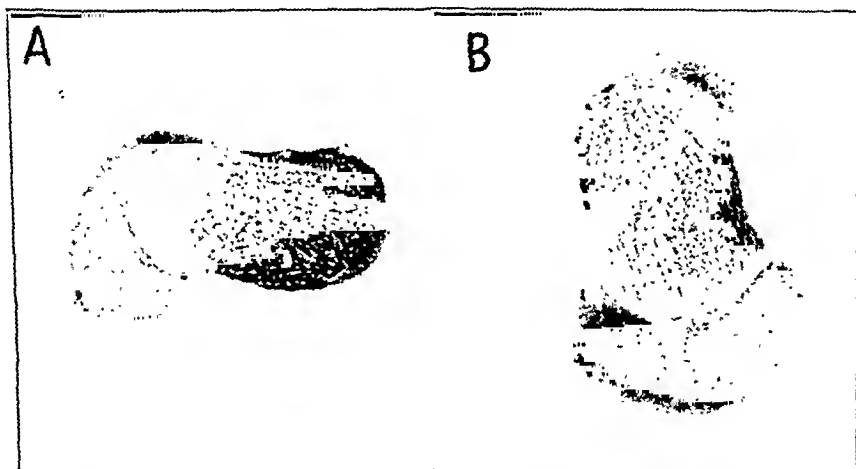


Fig. 5.—Roentgenograms: *A*, lateral view of an astragalus scraped clean of all ligaments. The ossification center stands out clearly; the cartilaginous portion is hazy. Injected material is seen in and about the periphery of the ossification center. None is evident in the cartilaginous portion. The majority of the vessels are in the neck region. *B*, anteroposterior view of the same specimen showing injected material in the bony nucleus, which is largely in the neck.

neck of the astragalus with no displacement. Their roentgenograms showed only a serrated line across the neck. None of these patients exhibited evidence of aseptic necrosis of the body of the astragalus at any time during the course of healing. All that was necessary in their treatment was immobilization. Case 14 illustrates their type of case.

**CASE 14. (*Incomplete Fracture of Neck of Astragalus*).**—A. J., a nurse 20 years of age, was thrown from a horse, catching her foot in a stirrup, and was dragged 30 feet (9 meters) on Oct. 3, 1931. Roentgen examination revealed incomplete fracture of the neck of the left astragalus. The left leg and foot were immobilized in a cast for ten weeks, and the patient used crutches for another six weeks. She returned to work in February 1932 and had no trouble thereafter. In February 1939, eight years after injury, motion in the ankle joint and subastragalar joint was normal. Roentgenograms showed a normal astragalus and normal ankle and subastragalar joints. She stated that she suffered no pain, did her regular work, played tennis and danced.



One patient who suffered incomplete fracture of the neck of the astragalus had a painful foot, with moderate restriction of motion in the ankle and subastragalar joints, one and one-half years after injury. Roentgenograms showed evidence of aseptic necrosis of the body of the astragalus and thinning of the cartilage space of both the ankle and the subastragalar joint despite the fact that the original injury produced no separation of the fragments (case 13).

**CASE 13** (*Incomplete Fracture of Neck of Astragalus, with Development of Aseptic Necrosis*).—F. L., an accountant 57 years of age, slipped and fell backward as he stepped up a high curbing on Feb. 9, 1938. Roentgenograms revealed incomplete fracture of the neck of the left astragalus without displacement. The foot and leg were immobilized in a cast for twelve weeks, and weight bearing was prohibited for seven weeks. In January 1940, two years after the injury, dorsiflexion of the ankle was restricted to 90/95 degrees and plantar flexion to 115/120 degrees. In the subastragalar joint inversion was restricted to 10/25 degrees and eversion to 5/10 degrees. Roentgenograms at this time showed aseptic necrosis of the body of the left astragalus and thinning of the cartilage space of both the

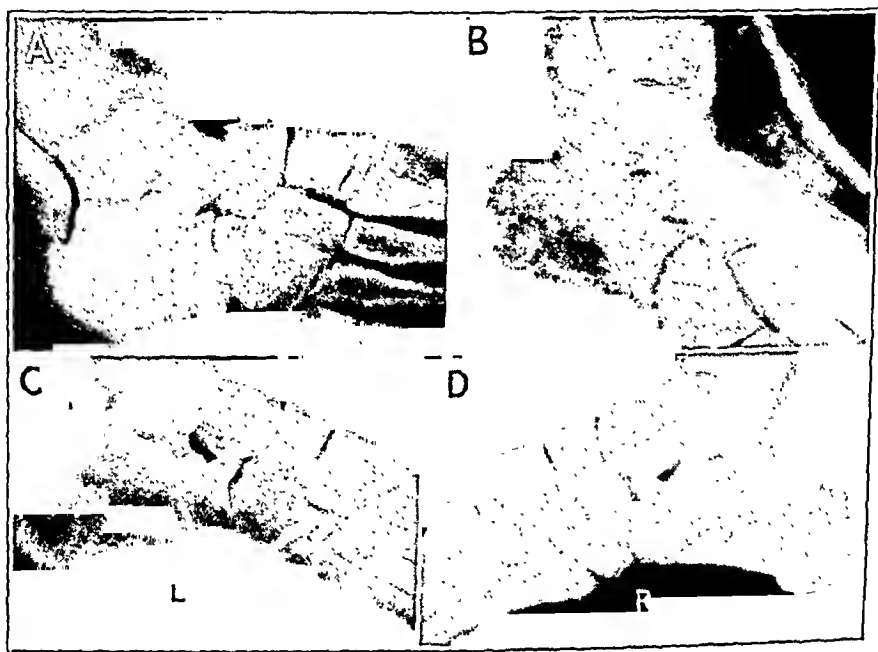


Fig. 6 (case 14).—Roentgenograms: *A*, incomplete fracture of the neck of the astragalus without displacement Oct. 3, 1931. *B*, foot in a cast Oct. 6, 1931. *C* and *D*, lateral views of the left (injured) and the right (uninjured) foot eight years after fracture (Jan. 16, 1939). There is no deformation or sclerosis of the astragalus.

ankle and the subastragalar joint. The patient complained of pain in the left foot after walking six blocks.

Six patients sustained fracture of the neck of the astragalus with only slight or moderate dorsal displacement of the neck fragment on the body. Closed reduction by manipulation followed by immobilization in plaster seemed adequate. All of these patients, despite the accuracy of the reduction obtained, exhibited aseptic necrosis in the proximal or body fragment during the course of healing. All in the end had painful foot and ankle and showed marked loss of motion in the ankle joint and the subastragalar joint. Roentgen studies of these patients revealed sclerosis of the body of the astragalus and thinning of the cartilage space of both the ankle and the subastragalar joint. One patient, a child, had severe deformation of the dome of the astragalus after this bone had gone through the complete cycle of avascular necrosis and revascularization (case 7).

**CASE 7** (*Fracture of Neck of Astragalus Treated by Closed Reduction and Immobilization*).—D. C., a child 6 years of age, jumped from the roof of a garage, alighting with the left foot turned in, July 6, 1936. On July 7, with the patient under anesthesia induced with ether, closed reduction was accomplished. The foot and leg were immobilized in a plaster cast for five months. Weight bearing was prohibited for fourteen months. Roentgenograms taken November 15, five months after the injury, showed aseptic necrosis of the body of the astragalus. On Jan. 6, 1939, two and one-half years after the injury, dorsiflexion of the left ankle was restricted to 70/90 degrees; plantar flexion, to 110/135 degrees. In the subastragalar joint inversion was restricted to 5/35 degrees and eversion to 0/15 degrees. Roentgenograms made in January 1939 showed complete revascularization of the astragalus, marked deformation of the astragalar body and marked thinning of the cartilage space of both the ankle and the subastragalar joint. The child had a marked limp and complained of severe pain.

It has been stated that accurate reduction insures good recovery. In 9 of the 12 patients in this group who exhibited aseptic necrosis of the astragalar body

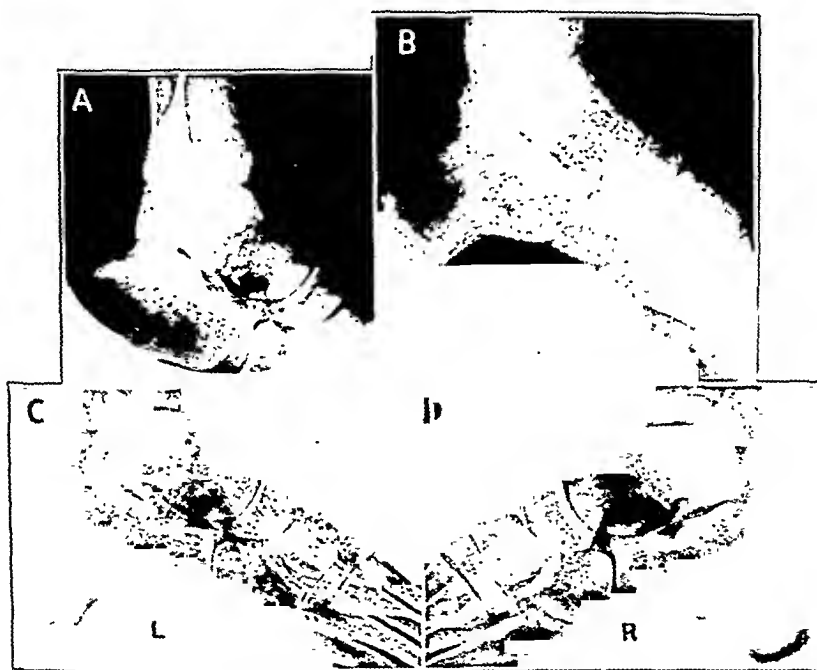


Fig. 7 (case 13).—Roentgenograms: *A*, incomplete fracture of the neck of the astragalus without displacement Feb. 9, 1938. *B*, fracture line partially obliterated four months after injury (June 25, 1938). The body of the astragalus is dense; the remaining tarsal bones are demineralized. *C*, lateral views of the left (injured) and the right (uninjured) foot one year after injury (Jan. 21, 1940). The fracture line is sclerotic. There is some evidence of revascularization in the body adjacent to the fracture line. The ankle joint space and the subastragalar joint space are not severely altered.

fragment perfect reduction was obtained and maintained. In 2 the position of the fragments was good, and in 1 patient the position was poor. This seems to prove that the accuracy of the reduction has little or no influence in preventing aseptic necrosis of the body. Of course, for a good functional result accurate reduction is a requisite of any intra-articular fracture.

Five patients required open reduction. All these patients had displacement of the body of the astragalus through the posterior part of the capsule. This made necessary complete removal of the posterior or body fragment. In all 5 patients

*Data on Patients with Fracture of the Neck of the Astragalus*

Patient	Age, Yr.	Degree of Separation of Fragments	Treatment	Accuracy of Reduction	Period of Observation	End Result			Pain
						Motion in Ankle Joint	Motion in Subastragalur Joint	Roentgen Findings	
1 E. J.	17	Complete posterior displacement of body of astragalus	Open reduction; complete removal and replacement of body	Excellent	1 yr. 6 mo.	Dorsiflexion and plantar flexion restricted 10°	Inversion restricted 10°; eversion, 5°	Union; dense sclerosis of body of astragalus, thinning of ankle and subastragalur joint spaces	++
2 D. H.S.	30	Complete posterior displacement of body	Open reduction; complete removal and replacement of body	Excellent	11 yr.	Dorsiflexion restricted 15°; plantar flexion, 30°	Inversion and eversion obliterated	Union; dense sclerosis of body of astragalus, marked thinning of ankle and subastragalur joint spaces, osteophytes on margin of ankle joint	+++
3 A. O.	12	Partial posterior displacement of body	Open reduction; complete removal and replacement of body	Good	2 yr.	Dorsiflexion and plantar flexion restricted 15°	Inversion restricted 30°; eversion obliterated	Nonunion; dense sclerosis of body of astragalus, marked thinning of ankle and subastragalur joint spaces	+++
4 O. K.	23	Complete posterior displacement of body	Open reduction; complete removal and replacement of body	Excellent	4 yr.	Dorsiflexion and plantar flexion obliterated	Inversion and eversion obliterated	Union; dense sclerosis of body of astragalus, thinning of ankle and subastragalur joint spaces, osteophytes on margin of ankle joint	+++
5 P. S.	50	Complete posterior dislocation of body	Open reduction; complete removal and replacement of body	Good	3 yr.	Dorsiflexion and plantar flexion restricted 10°	Inversion and eversion obliterated	Union; dense sclerosis of body of astragalus, marked thinning of subastragalur joint spaces	+++
6 B. H.	24	Complete posterior dislocation of body	Total astragalectomy	Position of foot good	2 yr.	Dorsiflexion restricted 25°; plantar flexion, 10°	.....	Good posterior displacement of foot on ankle mortise	+++
7 D. C.	6	Slight displacement of neck on body	Closed reduction	Excellent	2 yr. 6 mo.	Dorsiflexion restricted 20°; plantar flexion, 25°	Inversion restricted 30°; eversion obliterated	Union; complete cycle of aseptic necrosis and revascularization terminating in marked deformity of astragalus and marked thinning of ankle and subastragalur joint spaces	+++
8 W. O.	37	Slight displacement of neck on body; no dislocation of body	Closed reduction	Excellent	2 yr. 5 mo.	Dorsiflexion restricted 10°; plantar flexion, 5°	Inversion restricted 20°; eversion obliterated	Union; dense sclerosis of body of astragalus, moderate thinning of ankle joint space; marked thinning of subastragalur joint space, osteophytes on margin of ankle joint	+++

P	34	Modernite displacement of neck on body; no posterior dislocation of body	Closed reduction	Good	3 yr.	Dorsiflexion restricted 16°; plantar flexion, 5°	Inversion restricted 20°; eversion obliterated	Union; dense sclerosis of body of astragalus, marked thinning of ankle and subastragalar joint spaces	+
10	23	Slight displacement of neck on body; no posterior dislocation of body	Closed reduction	Excellent	2 yr.	Dorsiflexion restricted 5°; plantar flexion, 10°	Inversion and eversion restricted 10°	Union; dense sclerosis of body of astragalus, marked thinning of subastragalar joint space, slight thinning of ankle space	++
11	33	Moderate displacement of neck on body; no dislocation of body	Compound wound debrided and closed; manipulative reduction; body not removed	Poor	1 yr. 6 mo.	Dorsiflexion and plantar flexion obliterated; 15° equinus deformity	Inversion restricted 20°; eversion obliterated	Malunion; dense sclerosis of body; marked thinning of ankle and subastragalar joint spaces, marked deformity of astragalus due to poor reduction	+ + +
13	52	Moderate displacement of neck on body; no dislocation of body	Closed reduction	Excellent	1 yr. 6 mo.	Dorsiflexion restricted 5°; plantar flexion, 20°	Inversion and eversion obliterated	Union; dense sclerosis of body of astragalus; marked thinning of ankle and subastragalar joint spaces, slight varus of neck of astragalus	+ + +
14	57	No displacement of neck on body; incomplete fracture	Immobilization in plaster; no reduction necessary	Excellent	2 yr.	Dorsiflexion restricted 5°; plantar flexion, 5°	Inversion restricted 15°; eversion, 5°	Union; dense sclerosis of body of astragalus; marked thinning of ankle and subastragalar joint space	+ + +
14	20	No displacement; incomplete fracture	Immobilization in plaster; no reduction necessary	Excellent	8 yr.	Dorsiflexion and plantar flexion normal	Inversion and eversion normal	Union; no sclerosis of body of astragalus; no thinning of ankle or subastragalar joint spaces	0
15	21	No displacement; incomplete fracture	Immobilization in plaster; no reduction necessary	Excellent	2 yr.	Dorsiflexion and plantar flexion normal	Inversion and eversion normal	Union; no sclerosis of body of astragalus; no thinning of ankle or subastragalar joint spaces	0
16	18	No displacement; incomplete fracture	Immobilization in plaster; no reduction necessary	Excellent	1 yr. 6 mo.	Dorsiflexion and plantar flexion normal	Inversion and eversion restricted 5°	Union; no sclerosis of body of astragalus; no thinning of ankle or subastragalar joint spaces	0
17	8	No displacement; incomplete fracture	Immobilization in plaster; no reduction necessary	Excellent	2 yr.	Dorsiflexion and plantar flexion normal	Inversion and eversion normal	Union; no sclerosis of body of astragalus; no thinning of ankle or subastragalar joint spaces	0

the body was replaced with its cartilaginous surfaces intact. This group of patients presented the worst end results. All complained of severe pain and had marked restriction of motion in the ankle and the subastragalar joint. The roentgenograms

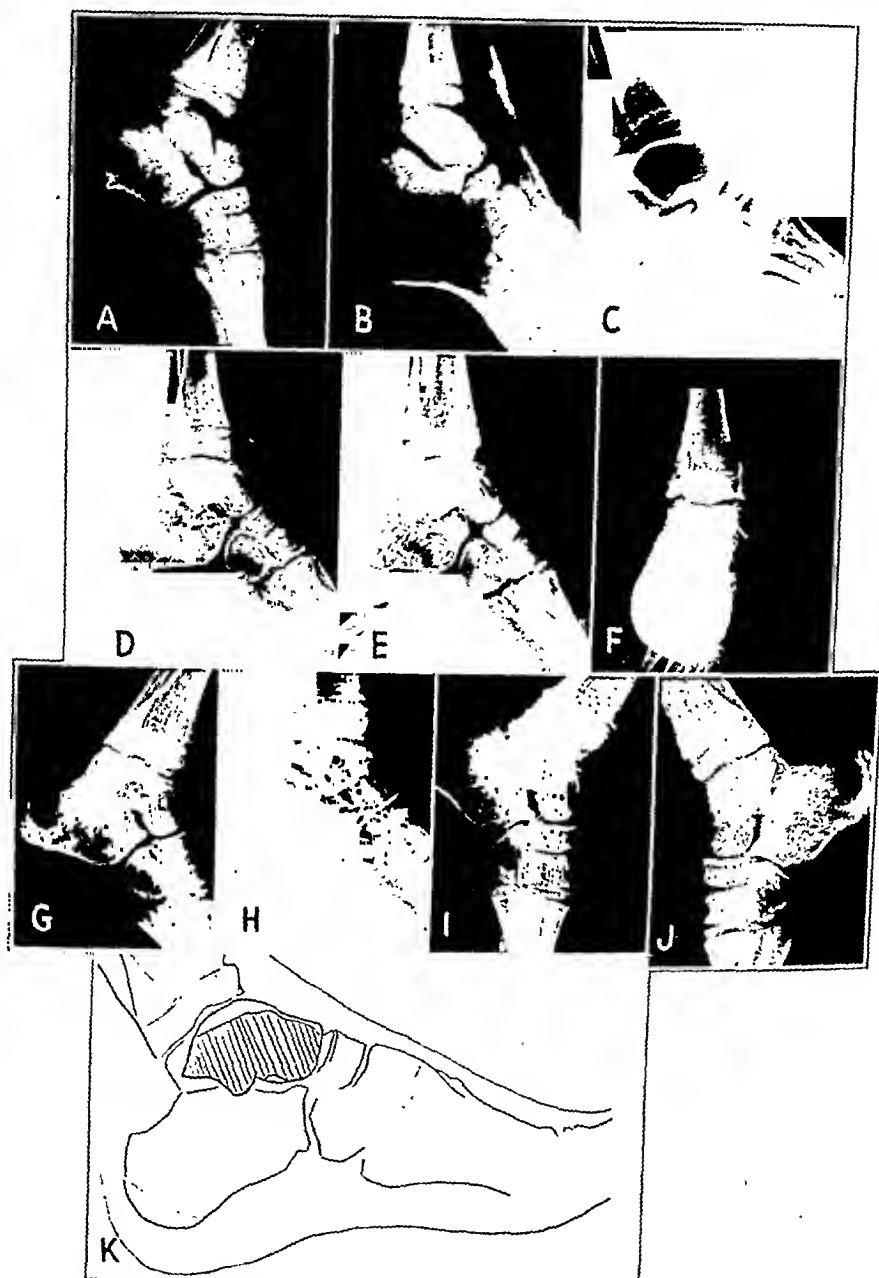


Fig. 8 (case 7).—*A*, fracture of the neck with displacement July 21, 1936. *B*, perfect anatomic reduction in cast July 27. *C*, foot eight weeks after injury (August 27). The body of the astragalus is dense; the remaining bones of the tarsus are demineralized. *D*, foot four months after injury (November 5). *E*, foot ten months after injury (May 1, 1937). There is deformation of the astragalus as well as narrowing of the ankle joint space. There is evidence of revascularization. *F*, anteroposterior view showing narrowing of the ankle joint May 1, 1937. *G*, foot eighteen months after injury (Dec. 1, 1937); further revascularization is seen. *H*, body deformed but with revascularization almost complete May 19, 1938. *I*, foot two years and six months after injury (Jan. 6, 1939). Revascularization is complete; the astragalus is deformed; the ankle and the subastragalar joint are narrowed. *J*, right uninjured foot of the same date for comparison. *K*, tracing with the left astragalus shaded superimposed on the right, showing the deformation of the bone during the revascularization.

of all revealed dense sclerosis of the body of the astragalus, marked thinning of the cartilage space of both the ankle and the subastragalar joint. Some had osteophytes on the margins of the ankle joint. Without exception, these patients were totally disabled for any activity requiring standing or walking. Case 1 is a case in point.

*CASE 1 (Fracture of Neck of Astragalus; Open Reduction, Complete Removal and Replacement of Body with Articular Cartilage Intact).—E. J., a roofer 17 years of age,*

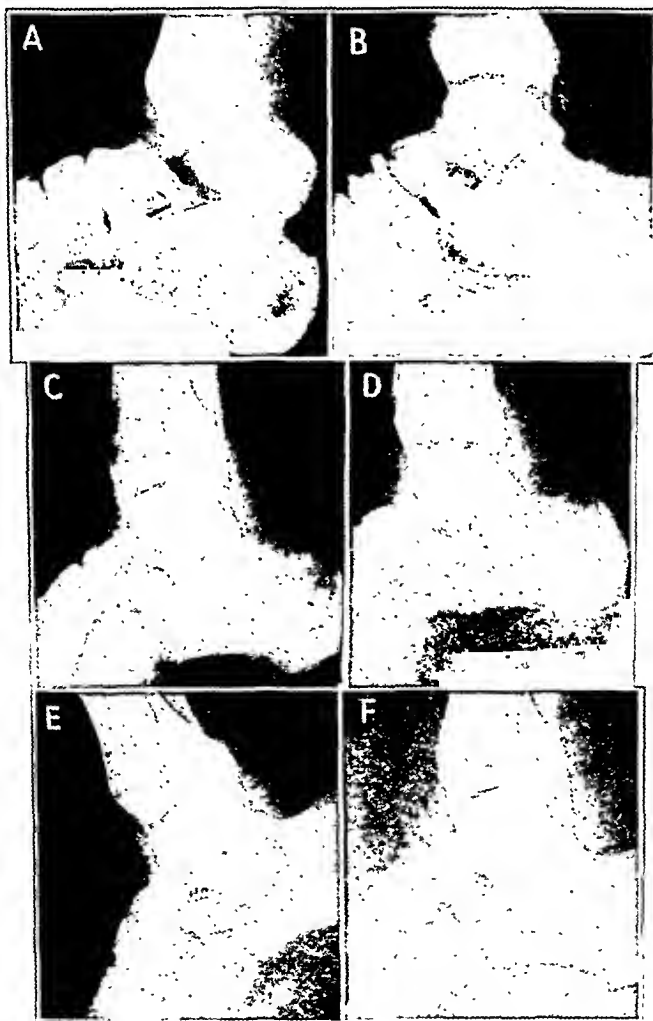


Fig. 9 (case 1).—Roentgenograms: *A*, fracture of the neck of the astragalus with posterior displacement of the body July 16, 1932. *B*, bones after open reduction and immobilization in plaster July 22. *C*, bones two months after injury (September 23). A good position is noted. The body is dense and not demineralized. *D*, bones four months after injury (November 30). The body of the astragalus is denser than the surrounding tarsal bones. The fracture line is indistinct. *E*, bones eight months after injury (April 1, 1933). There is definite devitalization of the body. *F*, bones seventeen months after injury (Feb. 2, 1934). The fracture line is not visible. There is no deformation of the astragalus. The ankle space and the subastragalar joint space are slightly narrowed. There is no evidence of revascularization of the astragalar body.

slipped from a ladder, falling 10 feet (3 meters) to concrete on July 16, 1932. Roentgenograms showed fracture of the neck of the right astragalus with marked posterior displacement of

the body. Closed reduction was attempted unsuccessfully on the day of injury. On July 22 open reduction was done. It was necessary to remove the body fragment from the ankle. The fragment was replaced with all cartilaginous surfaces intact. Convalescence was uneventful. Weight bearing was permitted six months after the injury. On Jan. 2, 1934, eighteen months after the injury, there was thickening about the ankle. Dorsiflexion of the ankle was restricted to 80/90 degrees. Plantar flexion of the ankle was restricted to 120/130 degrees; inversion of the subastragalar joint was restricted to 20/30 degrees; eversion of the subastragalar joint was restricted to 5/10 degrees. Roentgenograms showed dense sclerosis of the body of the astragalus and thinning of the cartilage space of both the ankle and the subastragalar joint. The patient complained of pain.

One patient was treated by total astragalectomy. Two years after the operation he was severely crippled and had fixed equinus deformity of the foot in spite of the fact that roentgenograms showed good posterior displacement of the foot in the ankle mortise.

#### COMMENT

The close parallel between fracture of the neck of the astragalus and fracture of the neck of the femur is evident. In both injuries the circulation to the proximal fragment may be and often is interrupted. Not even roentgen evidence that a fracture of the neck of the astragalus is incomplete or that the fragments are impacted gives absolute assurance of the integrity of the circulation. Aseptic necrosis of the proximal fragment will, as in the hip, occasionally result even under these conditions. With complete fracture aseptic necrosis of the body of the astragalus is the rule even though perfect anatomic reduction can be obtained and maintained by closed manipulative methods. If complete removal and complete replacement of the body are necessary because of marked displacement of the latter, death of the replaced fragment is inevitable.

The astragalus is almost completely covered by articular cartilage. On the normalcy of this cartilage depends the normal function of the ankle joint as well as that of the subastragalar joint. Articular cartilage degenerates when the bone underlying it undergoes aseptic necrosis. Thus, as a result of fracture of the neck of the astragalus, severe traumatic arthritis may develop in both the ankle and the subastragalar joint which will be relieved only by panastragalar arthrodesis. Panastragalar arthrodesis is useful but far from ideal. After a few years of usage the overstrained mediotarsal joints generally become the site of painful, disabling traumatic arthritis.

Clinical experience has proved that bony ankylosis of the subastragalar joint by itself is not disabling. For years the operation of triple arthrodesis has been carried out on feet, the articular cartilage being eradicated from the subastragalar joint, the astragaloscaphoid joint and the calcaneocuboid joint. No loss of motion in the ankle results from this type of operation. If restriction of ankle motion is desired, some modification of the operation, such as posterior bone block, the operation of countersinking described by Brewster or the angular resection outlined by Lambrinudi, must be done. As a result of the use of triple arthrodesis persistent aseptic necrosis of the body of the astragalus is extremely rare and ultimate thinning of the cartilage space of the ankle does not result.

In triple arthrodesis of the foot all the conditions which are present in complete fracture of the neck of the astragalus are present. In addition, however, there is complete ablation of the articular cartilage facing of the astragalus and of that of the calcaneus, so that spongy bone approximates spongy bone. Thus the cartilage barrier to the ingrowth of new blood vessels is removed.

It is felt that the grave disability which results from severe fracture of the neck of the astragalus warrants application of a principle which has been used in

surgical treatment of the foot for many years. It is probable that early subastragalar arthrodesis, by allowing more rapid revascularization of the body of the astragalus, would salvage many ankle joints, prevent many severe disabilities and do away with the necessity for late panastragalar fusions.

#### SUMMARY AND CONCLUSIONS

The literature on fracture of the neck of the astragalus reveals wide divergence of opinions concerning the intrinsic circulation in this bone, the best method of treatment for this fracture and the ultimate prognosis for the injury.

Studies of the vascular system by injection are presented, which seem to indicate that the vital blood supply to the astragalus enters the neck through the superior astragaloscaphoid ligament.

The end results in 17 cases of fracture of the neck of the astragalus are presented. Attention is called to the high incidence of aseptic necrosis of the body, which leads to degenerative arthritis in both the subastragalar joint and the ankle joint and the severe disability which this produces.

Complete removal and replacement of the body with all articular surfaces intact are condemned.

Attention is called to the fact that in a high percentage of cases of incomplete fracture of the neck of the astragalus the joints will recover without disability if protected. Occasionally, however, aseptic necrosis of the astragalar body may result even under these circumstances.

Perfect anatomic reduction and maintenance of perfect position, even when accomplished by simple manipulation, will usually be followed by aseptic necrosis of the body of the astragalus and severe disability in the ankle joint and the subastragalar joint.

It is suggested that the early erosion of the articular cartilage in the subastragalar joint may, by removing the cartilaginous barrier to the ingrowth of blood vessels, shorten the period for revascularization of the body and prevent extensive degeneration of the articular cartilage in the ankle joint.



## SKELETAL TRACTION AS A METHOD OF TREATMENT FOR CERTAIN FOOT DEFORMITIES

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The deformed feet which have been treated with skeletal traction include 52 recurrent club feet, 3 acquired club feet and 6 cavus feet. All the patients were children between the ages of 2 and 12 years and the deformed feet had been previously treated by various methods, with poor or inadequate end results.

In this particular age group the growth factor is important. Tissue change is rapid, and therefore any factors which tend to increase or to retard growth or to change in any way the normal direction of growth will produce a deformity.

Congenital deformities of the foot generally present a series of partial dislocations of the tarsal and midtarsal bones together with contractures of tendons and of interosseous ligaments. If these deforming factors are allowed to persist, the deformity will increase steadily with growth. The same is true of acquired deformities.

Taking into consideration the factor of growth, one may conclude that any method designed to correct these deformities should offer the least possible trauma to the involved tissues during the process of correction. The method should also insure that the correction be relatively quick and complete. Too vigorous attempts at correction may do irreparable damage to the cartilage surfaces and growth centers of the bones of the foot, and the soft tissues may be so badly torn that ruptured tendons and the resulting scar tissue may be secondary causes of deformity.

Skeletal traction as a means of correcting deformities of the feet offers a method which is relatively atraumatic and quick. The bones of the foot can be realigned and the soft tissues so stretched and softened that overcorrection can be obtained with only the slightest possible pressure. The time required to achieve this varies from three to four weeks.

The successful application of skeletal traction to a foot depends on having three fixed points from which to apply the necessary push and pull to get correction of the deformity. These fixed points are obtained by inserting Kirschner wires through the tibia, the os calcis and the necks of the metatarsal bones. The wire through the tibia should be at a convenient distance from the os calcis so as to allow room for the distracting rods. It is usually inserted at the junction of the upper and middle thirds of the tibia. There should be as much bone as possible ahead of the wire in the os calcis, and the wire is therefore inserted close to the posterior superior surface. The wire through the metatarsal bones should engage all the bones, particularly the first and the fifth. These three fixed points are then joined together with distracting rods or turn buckles.

When the apparatus is correctly fitted to the foot, it is possible to apply distraction in the direction of the long axis of the foot and in the direction of the long axis of the tibia (fig. 1). In this manner the contracted soft structures of the foot and the contracted heel cord are so stretched that when the apparatus is removed no force is required to put the tarsal bones into an overcorrected position. No distraction or tension should be applied for several days after the application of the apparatus. If this principle is not followed, the patient is quite uncomfortable and there is likely to be considerable edema of the foot. At

the end of three days, when the patient has become accustomed to the apparatus, distraction is begun. This must be carried on gradually and not beyond the point of discomfort. The rod joining the wire through the metatarsal heads and the wire through the tibia is used as a stabilizer for the apparatus and not for traction or distraction except in the case of a congenital calcaneovalgus deformity. It is then used to push the forefoot into a slight equinus position. If traction is used to dorsiflex the forefoot, it is easy to partially dislocate the forefoot at midtarsus and produce a rocker foot (fig. 6B). Three or four weeks are required to get complete stretching. The apparatus is then removed and the foot put in an over-corrected position in a plaster cast and kept in this position from four to six months. Figure 2 shows a typical recurrent congenital equinovarus deformity before and after stretching by skeletal traction.

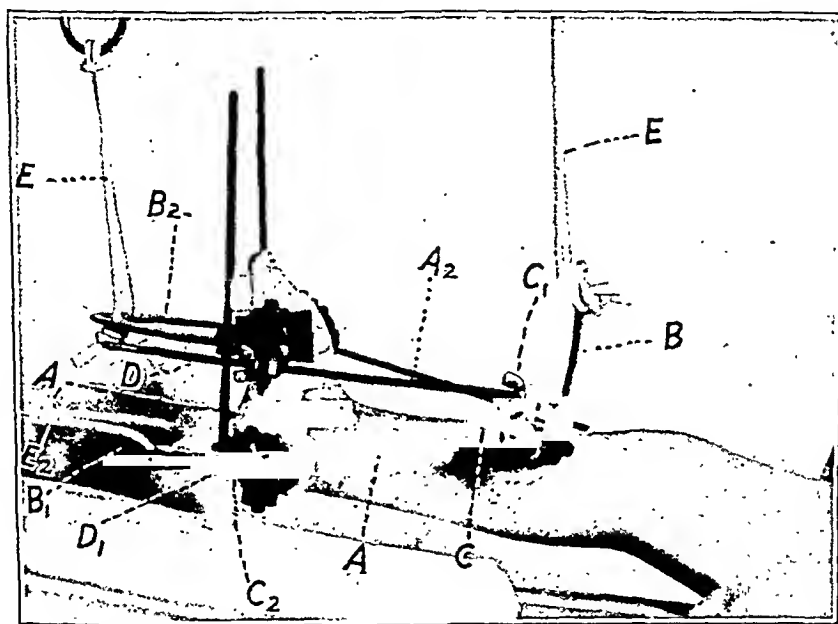


Fig. 1.—Apparatus for skeletal traction: *A*, *A*<sub>1</sub> and *A*<sub>2</sub> indicate threaded distracting rods; *B*, *B*<sub>1</sub> and *B*<sub>2</sub>, horseshoes holding the Kirschner wires; *C*, *C*<sub>1</sub> and *C*<sub>2</sub>, wing nuts for obtaining distraction or adjustment of the apparatus; *D* and *D*<sub>1</sub>, screw nuts for controlling the distracting of the forefoot; *E*, *E*<sub>1</sub> and *E*<sub>2</sub>, suspension cords controlling the entire leg while the patient is in bed.

The immediate results of the use of this method of treatment show that over-correction of the deformity was obtained in all cases but 1. The failure in that instance was due to the fact that so much damage had been done to the bones of the foot during previous treatment it was impossible to change the fixed alinement. The end results as seen during the follow-up period were not as satisfactory as the immediate results.

Over a period of seven years it was found that 65 per cent of the recurrent congenital equinovarus feet, 50 per cent of the acquired equinovarus feet and 50 per cent of the cavus feet were completely relieved of the deformity.

Failure to maintain permanent correction of the deformity in the group of congenital equinovarus feet was due mainly to the fact that previous treatment had so damaged the tarsal bones that it was impossible to keep them in alinement as

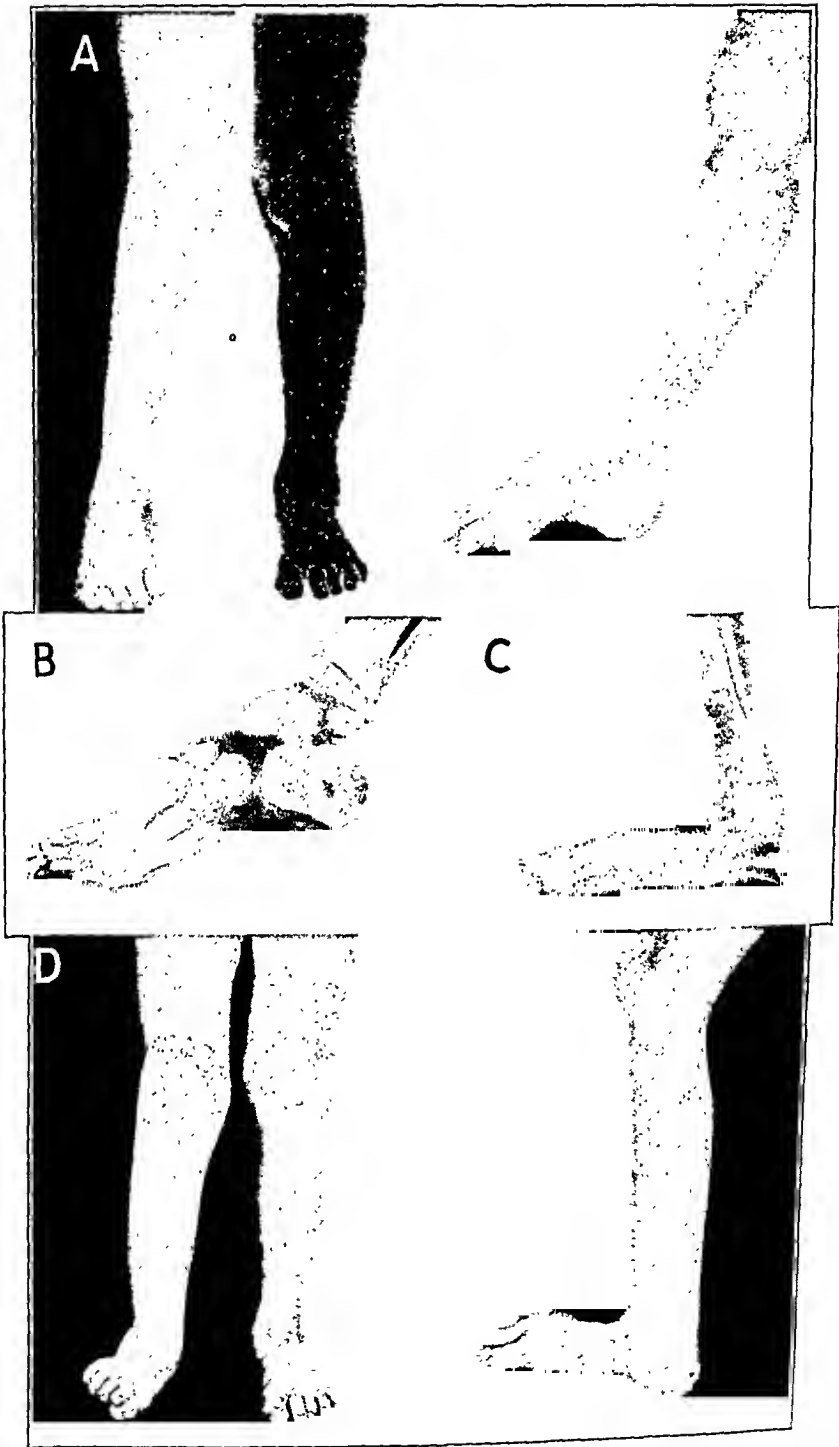


Fig. 2.—*A*, cavus foot in an equinus position with inversion of the os calcis and adduction of the forefoot. *B*, roentgenogram showing the abnormal relation between the astragalus and the os calcis. The astragalus is partially dislocated forward. *C*, roentgenogram showing the astragalus within the ankle mortise and an improved relation between the os calcis and the astragalus. The foot now has the appearance of a flat foot. *D*, right foot in a good over-corrected position.

the foot enlarged with growth. The deformity therefore slowly recurred, so that these patients subsequently had their feet stabilized by triple arthrodesis. In a small percentage of these patients the failures were due to indifferent after-care on the part of the parents and incomplete correction following stretching. In these cases restretching by skeletal traction gave complete relief from the deformity.

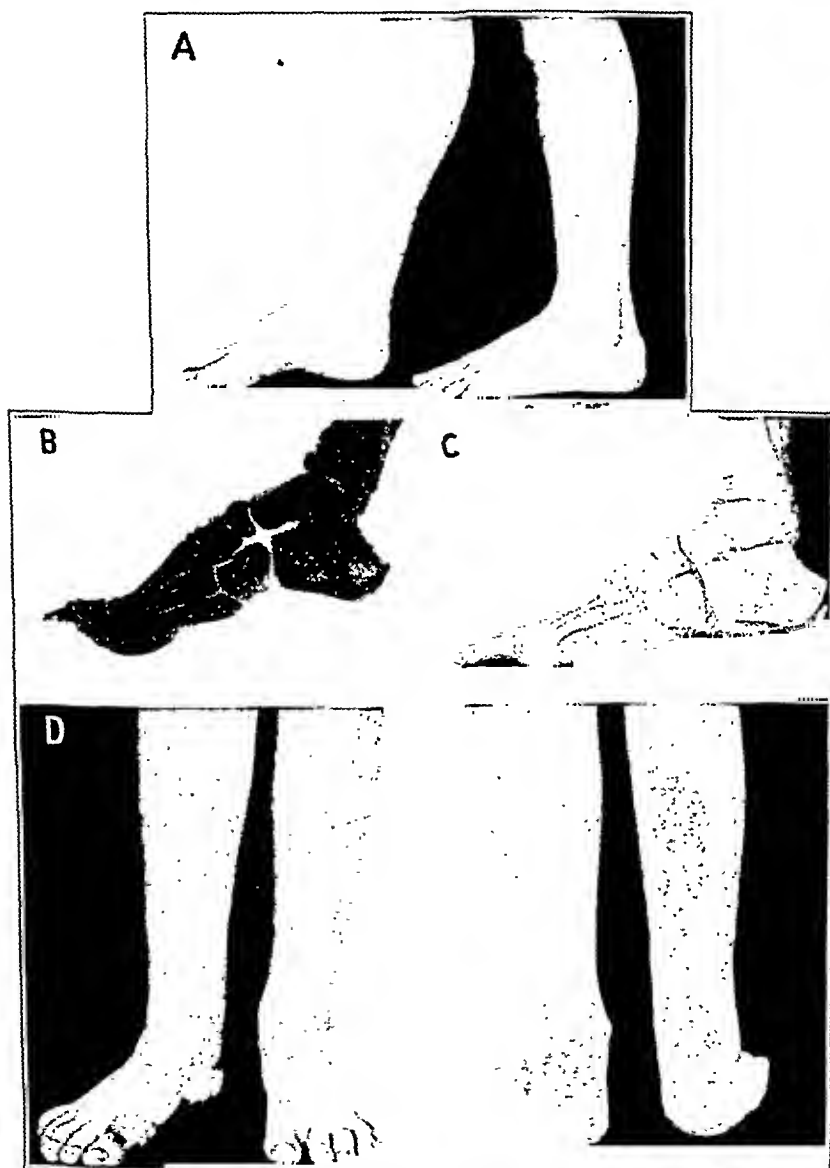


Fig. 3.—*A*, cavus deformity of the right foot. *B*, roentgenogram showing the cavus deformity with a moderate amount of hammer toe deformity. *C*, roentgenogram showing a flattening of the bony arch of the foot with a decrease in the hammer toe deformity. *D*, cavus deformity and hammer toe deformity entirely corrected.

In the group of acquired equinovarus feet the deformity was due to contracture secondary to anterior poliomyelitis, and the correction of the deformity was undertaken purely as a temporary measure. Correction was not difficult in this group, and the feet were held in neutral or overcorrected position until such time as

it was possible to balance the foot by muscle transplants or stabilize it by triple arthrodesis. In 1 case, however, the muscle power returned following correction, and no further intervention was necessary to maintain a well balanced foot.

Although the initial results of stretching in the cavus feet were good, the end results were only 50 per cent satisfactory. The feet in which the correction was maintained permanently were those with only a mild degree of deformity (fig. 3).

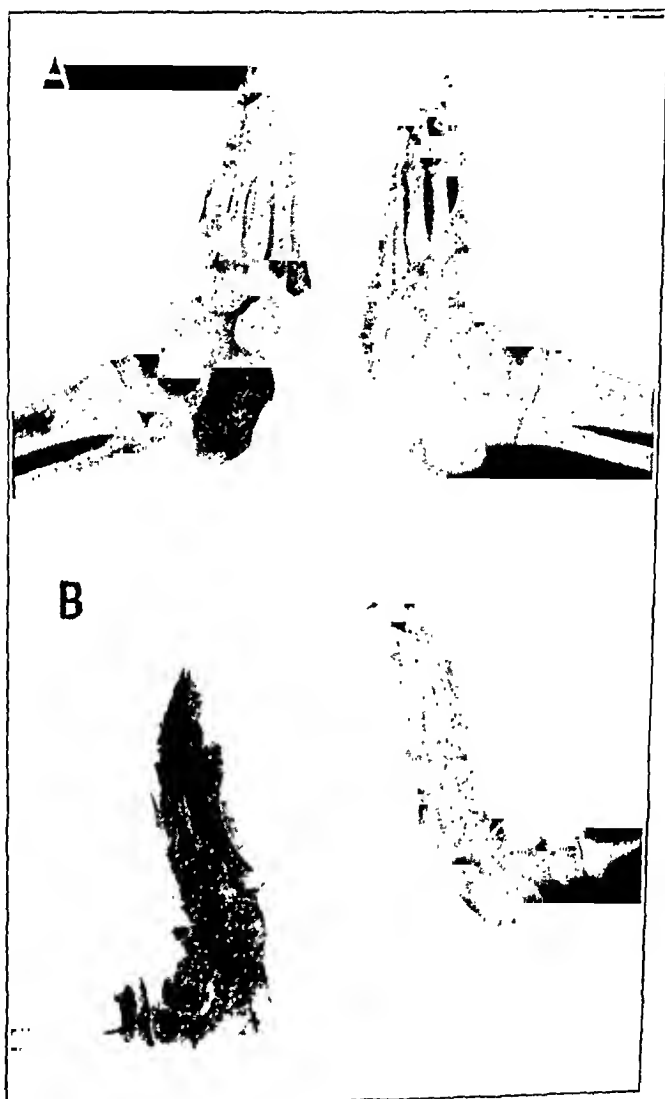


Fig. 4.—*A*, roentgenogram showing deformity of both astragali, rocker deformity of both feet and an extreme equinus position of each os calcis. This illustrates the condition of the feet after various methods of correction had been attempted. *B*, roentgenogram showing the result after skeletal traction had been used. Note that each os calcis is still in the equinus position, that the rocker deformity has been increased and that the scaphoid bone of the left foot is dislocated dorsally. The failure to obtain correction in these feet was due to the marked deformity of the tarsal bones before traction was applied.

In the cases in which the contractures were more severe, permanent correction was obtained by a combination of plantar fasciotomy and Steindler stripping in conjunction with skeletal traction.

The results of too vigorous treatment prior to the application of skeletal traction were clearly demonstrated in the group of patients in which failure ultimately led to triple arthrodesis.



Fig. 5.—*A*, roentgenogram showing the relation between the astragalus and the os calcis prior to manipulation of the foot. *B*, roentgenogram showing dislocation of the astragalus out of the ankle mortise. The head of the astragalus is pointing toward the plantar surface of the foot. This is the result of too forceful manipulation.

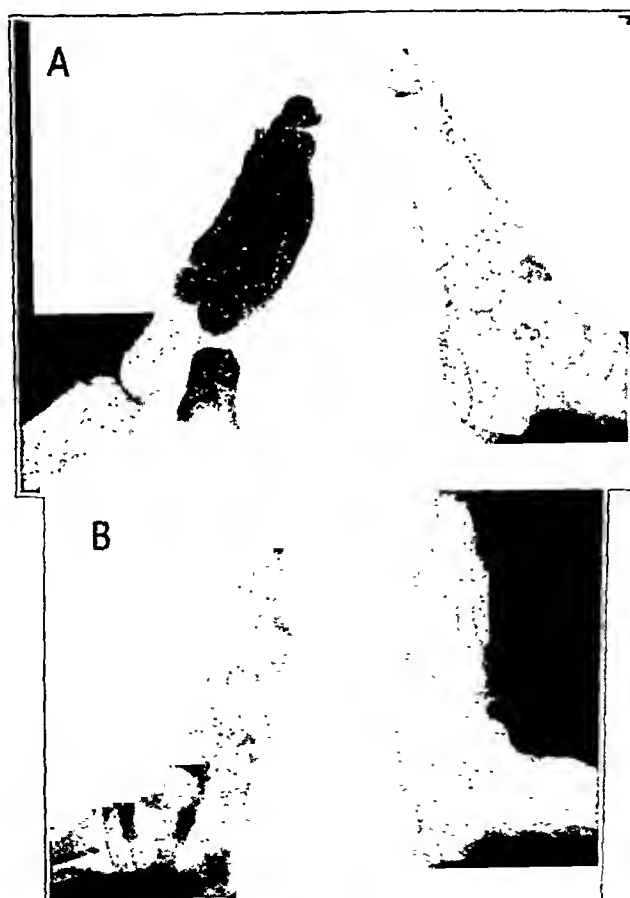


Fig. 6.—*A*, roentgenogram showing partial dislocation of the astragali of both feet. It also shows some flattening and deformity of the superior articulating surface of each os calcis. *B*, roentgenogram showing both astragali in better relation with the ossa calcis. Each astragalus is within the ankle mortise. The right foot shows a mild degree of rocker deformity. This was caused by too much traction on the forefoot in dorsiflexion.

Figure 4 *A* shows the condition of a patient's feet after five and a half years of manipulation and surgical treatment. The child had had four manipulations under anesthesia induced with ether, followed by stripping of the ligaments from the medial side of the os calcis and the plantar surface of the foot. Clinical examination prior to stretching by skeletal traction showed rigid equinus and rocker foot deformities of both feet. Figure 4 *B* shows that skeletal traction failed to alter the deformity in any way, and triple arthrodesis was performed before the patient was able to walk with any degree of comfort. Figure 5 shows dislocation of the astragalus out of the ankle mortise. The head of the astragalus is directed toward the sole of the foot. The dislocation was the result of too forceful manipulation.

In every case of recurrent congenital equinovarus deformity the astragalus was shown by roentgenogram to be partially dislocated forward from the ankle mortise and the superior articulating surface of the os calcis. In many cases roentgen examination showed that the superior articulating surface of the astragalus had been flattened, with evidence of destruction of cartilage (fig. 6).

In some of the cases in which triple arthrodesis was subsequently required, it was shown at operation that the articulating surfaces of the head of the astragalus and the posterior articulating surface of the scaphoid were so deformed that it was anatomically impossible to fit them together in a stable position. This condition of the articulating surfaces cannot be demonstrated by roentgenogram, but it is believed to be one of the chief factors of recurrence after apparent complete overcorrection.

#### SUMMARY

Of the 61 deformed feet treated by skeletal traction, all but 1 have been successfully corrected.

Failure to maintain correction in 40 per cent of the feet treated was due mainly to gross deformity of the tarsal bones secondary to too vigorous previous treatment.

In a few cases failure to maintain correction was due to incomplete overcorrection following stretching by skeletal traction.

It is not suggested that skeletal traction in itself is a cure for deformities of the foot. It has, however, been shown that skeletal traction provides a means for overcorrecting the contractures associated with these deformities, thereby making it possible to aline the articulating surfaces of the bones of the foot in an overcorrected position with the least amount of trauma in a relatively short time.

Maintenance of correction depends on (*a*) completeness of overcorrection following stretching and (*b*) holding the foot in overcorrection for a sufficiently long period.

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# SUBTROCHANTERIC OSTEOTOMY IN COXA VARA

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DETROIT

In the relief of many types of disability of the hip, realinement of the femur after this bone has been divided at its upper extremity in a variety of ways has been widely and increasingly practiced over more than half a century. The original subtrochanteric osteotomy of Gant became even more appreciated in England and this country through the example of its utilization set by Sir Robert Jones. At this stage of orthopedic development the simple osteotomy was limited to the rigid or presumably rigid hip with which, after division of the bone, the desired attitudinal correction could be obtained simply by realining the limb with the body.

Subsequently have come various technics for performing osteotomy under a movable hip joint, including the bifurcation operation of Lorenz,<sup>1</sup> the wedge resections of Pauwels<sup>2</sup> and Schanz,<sup>3</sup> later made more exactly controllable by Riedel<sup>4</sup> and Gaenslen<sup>5</sup> through the use of externally held pins, and the horizontally displacing osteotomies of Hass<sup>6</sup> and McMurray. All these have in common the attainment of a new axial relation between the shaft and the head of the femur for the relief of either structural instability or deformity. For the deformity of coxa vara the Riedel-Schanz procedure has come to be a technic of adequate adaptability and precision in a majority of cases.

However, it has been my experience that certain conditions are met in which this osteotomy as so far developed fails to meet the needs quite properly. Accordingly, a further technical modification has been worked out that has been so gratifying as to seem to warrant description. The two conditions encountered are, respectively, congenital coxa vara and adolescent coxa vara of high degree.

Congenital coxa vara, while not a frequently encountered condition, has been in its severe forms a rather difficult one to manage toward a satisfactory outcome. The varying manifestations of the lesion are well illustrated in the history of 3 siblings. (Incidentally, this is the single instance of siblings with congenital coxa vara in my experience.) In the first sibling the lesion was unilateral, the dystrophy or dyscrasia of the epiphysial area was mild, and by the judicious use of casts and non-weight-bearing appliances the femoral neck was carried along to approaching maturity and consolidation with only moderate varus deformity, which was quite easily offset by small wedge osteotomy; in other words, the moderate coxa vara was readily convertible to coxa valga, with termination of the difficulty.

The second sibling at the age of 8 years had acquired bilaterally a 90 degree deformity, with the epiphysial plate still much disorganized and unstable. Osteotomies decreased the deformity, but technical difficulties prevented complete conversion to coxa valga, and the deformity recurred. In such a case of bilateral deformity one may infer that surgical epiphysiodesis would have prevented recurrence, with equality of the legs in length. But it is my thesis that if in this disorder

1. Lorenz, A.: *Wien. klin. Wchnschr.* 49:41, 1919.

2. Pauwels, F.: *Ztschr. f. orthop. Chir.* 51:125, 1929; *Der Schenkelhalsbruch, ein mechanisches Problem*, Stuttgart, Ferdinand Enke, 1935, p. 6.

3. Schanz, A.: *Arch. f. klin. Chir.* 83:336, 1907.

4. Riedel, G.: *Zentralbl. f. Chir.* 57:84, 1930.

5. Gaenslen, F. J.: *J. Bone & Joint Surg.* 17:76, 1935.

6. Hass, J.: *Ergebn. d. Chir. u. Orthop.* 21:457, 1928.



the shearing strains of the position of coxa vara can be replaced by the axial stress of coxa valga, the epiphysial plate will spontaneously become stabilized and go on to normal fusion.

Sibling 3 suffered from an even greater degree of dystrophy. Though the condition was recognized and conservative treatment applied, complete solution of continuity developed in one hip, and in the other the deformity in the femoral

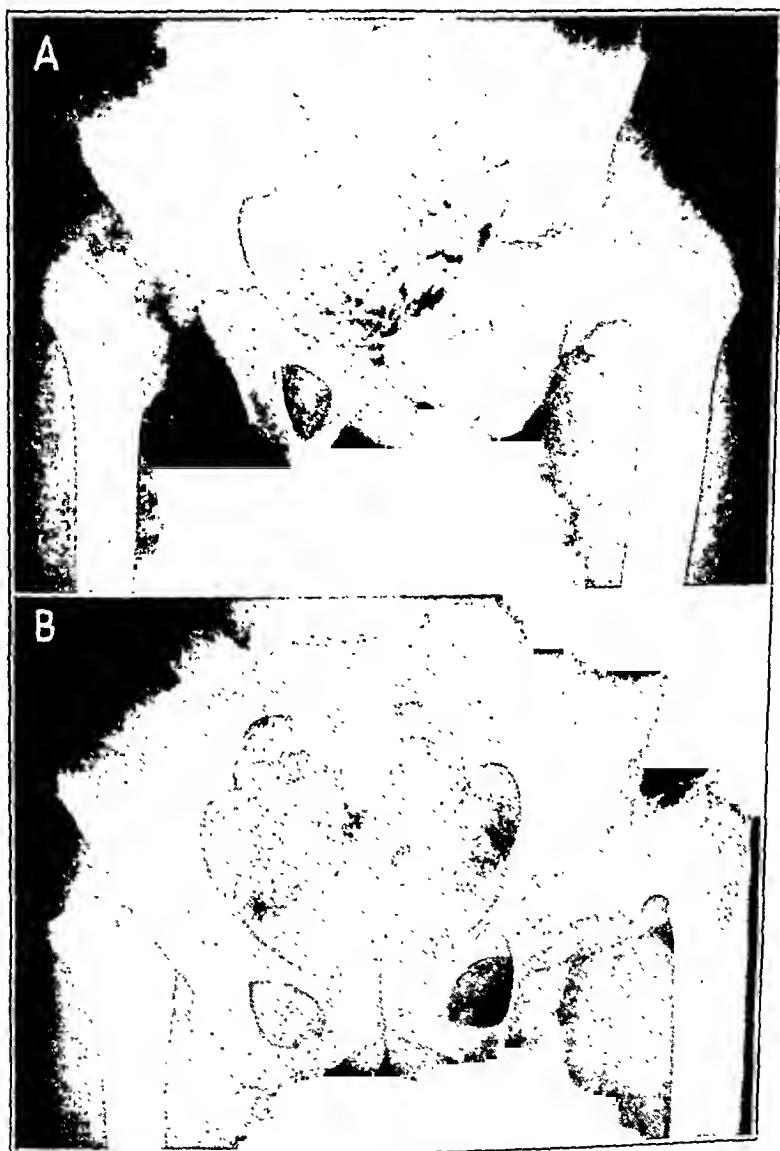


Fig. 1.—*A*, bilateral congenital coxa valga at the age of 8. A 90 degree deformity is present on the left side, with a vertical epiphysial plate, and on the right side there is dissolution of continuity, with a shadow (faint) of the undeveloped head in the lower part of the acetabulum.

*B*, same hip as in *A* at the end of the period of growth with practically no bearing of weight for a five year period and a Colonna type of reconstruction reported. The patient showed a bad gait, and future disability was certain. The deforming tendency in the left hip was uninfluenced by protracted abduction in a cast.

neck progressed to an acute angle (fig. 1 *A* and *B*). Both hips eventually required a pseudarthrotic type of reconstruction, with inevitably greatly impaired function.

Other instances of complete epiphysiolysis at an early age in this disorder have been encountered by me, and most surgeons will recall such instances (fig. 2).

In going over a considerable series of end results from osteotomies in cases of this condition it was quite obvious that in those cases in which the degree of deformity permitted conversion to coxa valga the difficulty was uniformly terminated, while in those in which less correction was obtained and shearing strains persisted, some degree of recurrence was the rule.

The problem, then, in severe congenital coxa vara seemed to involve (1) use of a technic preventing untoward displacement in the correction of a high degree of deformity by osteotomy and (2) stabilization of the epiphysial area at an early age. In some of the clinics where these cases have been encountered, the latter factor has logically been regarded as of primary concern, and epiphysiodesis by drilling or grafting has been the primary step, with correction of the deformity by osteotomy following later. Closure has been obtained fairly readily in the older chil-



Fig. 2.—Congenital coxa vara going on to complete dissolution of continuity at the period of adolescence. The patient went elsewhere for reconstruction. The details of the case prior to treatment are unknown, but casts were used.

dren but in the younger ones the operation has usually failed of this achievement, with consequent progression of deformity. On the other hand, evidence seems to be accumulating, as one of the illustrated cases demonstrates, that the active chondral dystrophy and instability of prenatal origin are limited to the infantile years, after which instability is residual only in the presence of shearing strains. Therefore, if the latter element can be entirely eliminated or, better still, be replaced by axial stress, the epiphysial plate can be left to mature naturally, with as much consequent contribution to length of leg as may occur, which is of more importance in the cases of unilateral deformity.

Now, with the frequent necessity of a corrective shift of the longitudinal axial relations between the neck and the shaft of up to 90 degrees, it can be seen that after division of the bone the thigh will have to be abducted to at least a right angle with the pelvis before movement of the femoral neck has been checked in the hip joint and the new alignment secured. In any but young infants this range is impossible because of soft part restriction mesially in the thigh unless such a

pins by extending it through the trochanter into the ilium until the divergent lower pin became properly aligned with it as the correction at the site of osteotomy occurred.

Now as to the modification of the osteotomy itself. It is designed, as suggested, to add no shortening or loss of substance whatever, and in consequence of the conversion of the coxa vara into a coxa valga the limb is appreciably length-



Fig. 5.—*A*, old reduced congenital dislocation with acquired coxa vara and shortening of the femoral neck and some difference in length of the leg: (1) preoperative; (2) following center pivot osteotomy with conversion to coxa valga and increase in length of the leg.

*B*, end result in hip shown in *A*. Note excellent clinical stability without shortening.

ened and the preexistent shortening overcome. In fact, in a case of unilateral deformity the limb may then be slightly longer than the normal one, which is desirable, since in this disorder the capital epiphysis will mature and close somewhat prematurely anyway.

## TECHNIC

From the usual paper pattern of the femur, the pattern of the small wedge resection and protractor patterns of the angles of the Riedel pins have been made, duplicated in tin or aluminum and sterilized with the kit. A curved incision, belly anterior, extends from over the tip of the great trochanter to the level of junction of the middle and upper thirds of the shaft. With the dissection following intermuscular planes, the vastus lateralis muscle is stripped from both the lateral and the anterior aspect, exposing the anterior intertrochanteric region from the greater to the lesser trochanter, and a curved elevator is inserted close to the latter, exposing this area at the base of the neck (fig. 3 *A*).

The next step can be done with a sharp osteotome in the case of smaller children; otherwise, with a Jones hip saw; best of all, with the Cayo stab saw (motor). A diagonal cut in the bone is made laterally and proximally from the mesial cortex at an angle of 45 degrees to the shaft, ending at or a little mesial to the midpoint of the intertrochanteric line. Guided by the metal protractor patterns the two Riedel pins are then inserted, the upper one deeply through the neck and head, the second below in the shaft. With motor saw or osteotome, the wedge is then removed laterally, but, unlike the Schanz osteotomy, the wedge resection has its apex at about the midpoint of the bone, almost meeting, at this point, the upper end of the first saw cut. The result of course is a central pivot point on which the femoral shaft moves as the thigh is abducted and the wedge resection gap is closed up, with an opening up of the mesial saw cut as this realinement is secured, but with the shaft safe against mesial displacement from the chevron-like shape of the proximal side of the osteotomy. I use a two plate clamp on the order of a woodworker's vise instead of the Riedel plate to secure the two pins in their new relations. With the osteotomy stabilized under direct vision and pin control, it has seemed advisable to back out the proximal pin until it engages in head and neck only before the clamp is applied. The removed wedge is then impacted into the opened mesial cut and the wound closed. Plaster fixation can now be applied in any comfortable position, and further abduction is neither necessary nor wise. Consolidation of the osteotomy has been seen to occur very rapidly; in a 7 year old child, in only four weeks (fig. 3 *B*).

In dealing with acquired or adolescent coxa vara, deformity of so high a degree is not often encountered; on the other hand, as these conditions are usually unilateral, and already attended by some shortening, it has seemed desirable to avoid the further shortening of a considerable-sized full transverse wedge resection and apply the pivotal osteotomy technic here too, obtaining also its security against an undesired mesial displacement of the femoral shaft in the realinement. Two illustrations of this are shown, one of an old slipped epiphysis and the other of an old reduced dislocation followed by an acquired coxa plana and abduction block (figs. 4 and 5).

## SUMMARY

I have advanced the thesis that severe congenital coxa vara may be treated by converting it into coxa valga and have described a gratifyingly adequate technic for a subtrochanteric osteotomy peculiarly well adapted to securing wide ranges of stable, precise correction in this disorder and in other types of coxa vara. In arriving at this technic I have seemed conscious of the teaching and the practice of Robert Bailey Osgood in regard to methods of precision in the surgical correction of deformities of joints.

# PAGET'S DISEASE WITH ASSOCIATED OSTEOGENIC SARCOMA

## REPORT OF THREE CASES

MAURICE M. PIKE, M.D.

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I propose to discuss briefly the occurrence of osteogenic sarcoma as a complication of Paget's disease of bone. I may say at the beginning that I have a vivid recollection of Dr. Harvey Cushing's presenting such a case to a group of students during a third year medical course in surgery, the site of the sarcoma being the superior aspect of the skull and the patient an elderly woman. That case was followed to its termination at the Peter Bent Brigham Hospital during the school year, and I recall that at that time Dr. Cushing advised us that sarcoma occurred as a complication of Paget's disease in 7 per cent of the cases. It is noted that Geschickter and Copeland<sup>1</sup> in their book "Tumors of Bone" stated that this complication occurs in from 5 to 7 per cent of cases of Paget's disease. In a recently published volume on roentgenology, the English authors Shanks, Kerley and Twining<sup>2</sup> stated that sarcoma is a complication in 7 per cent of the cases. Geschickter noted that the sarcoma is usually of the periosteal type and may be osteolytic, cartilaginous or osteoblastic in nature. At the Hartford Hospital from 1937 through 1941 there were 53 recorded cases of Paget's disease of bone with associated sarcoma in 4 of them. This would give an incidence of 8 per cent.

The 3 cases which I shall report and which occurred within a period of a year and a half at the Hartford Hospital show for the most part an osteolytic type of osteogenic sarcoma. All 3 patients received rather extensive treatment with roentgen rays. In spite of this, metastases and extensions occurred, and death resulted after a varying period, with an extremely uncomfortable terminal stage, in all instances.

## REPORT OF CASES

CASE 1.—C. C., a 53 year old man, was referred to the hospital with symptoms related to the region of the left hip. His symptoms extended back over a period of ten months, with swelling and pain in the left leg. Previously the condition had been diagnosed as arthritis. Roentgen examination revealed Paget's disease generalized throughout the skeleton with a destructive lesion in the region of the lesser trochanter of the left femur, involving the left side of the sacrum. These findings in the pelvis may be noted in figure 1 A. The patient had definite secondary anemia, with phosphatase activity considerably elevated. Open biopsy of the lesion in the lesser trochanter was performed, the wound being closed without drainage. The pathologic specimen may be seen in figure 2. Multinucleated giant cells may be noted, with cells varying markedly in size and shape. The patient was given a course of treatment with high voltage roentgen rays, with which he had considerable local reaction of the skin. There was no relief from pain, and he gradually failed and died nine months after admission to the hospital or nineteen months after the onset of his symptoms.

1. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, New York, American Journal of Cancer, 1931.

2. Shanks, L. C.; Kerley, P., and Twining, E. W.: A Text-Book of X-Ray Diagnosis, London, H. K. Lewis & Co., Ltd., 1939, vol. 3.

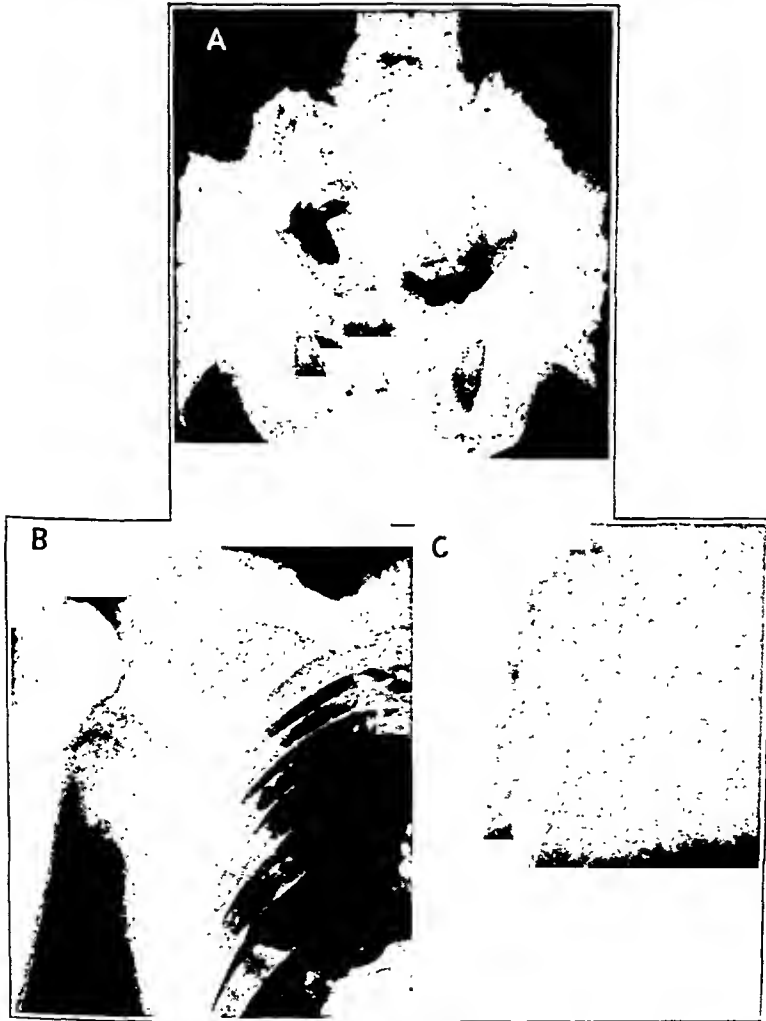


Fig. 1.—Roentgenograms in cases 1, 2 and 3: *A* (case 1), pelvis in Paget's disease. Note tumor of the left lesser trochanter involving the left side of the sacrum. *B* (case 2), left shoulder. Note destruction of bone in the humerus and the scapula. Note calcification within the tumor mass. *C* (case 3), right hip. Note marked destruction with large tumor mass.

CASE 2.—F. M., a man of 62 years, was admitted to the medical service of the hospital as a patient with cardiac disease and was found to have generalized Paget's disease with a tumor mass at the proximal end of the left humerus. He had complained of pain in the left arm for but one or two months but there had been pain in the chest for a period of one year. Roentgenograms revealed Paget's disease, the appearance of the skull being typical of involvement by that disease. Figure 1 *B* shows a roentgenogram of the left shoulder taken four months after the patient's admission to the hospital, revealing destruction of bone in the humerus and the scapula and a tumor mass in the supraspinatus region of the shoulder and calcification within the tumor mass. Figure 3 shows a low power projection of a



Fig. 2 (case 1).—Biopsy tissue from left greater trochanter. Note multinucleated giant cells.

section of the pathologic specimen from this patient's shoulder, revealing the occurrence of giant cells and many-shaped cells and destruction of bone all going on in the same field. This patient failed to respond to roentgen radiation, continuing to decline and succumbing eleven months after he was first seen in the hospital, fifteen months after the onset of symptoms in the left shoulder and twenty-three months after the onset of pain in the chest. There was also marked elevation of phosphatase activity. The blood levels of calcium and phosphorus were normal. There was definite secondary anemia, as noted in the preceding patient.

CASE 3.—M. E., a Negro woman of 63 years, came to the hospital because of a pathologic fracture of her right hip. She gave an interesting history of having had pain in the right leg

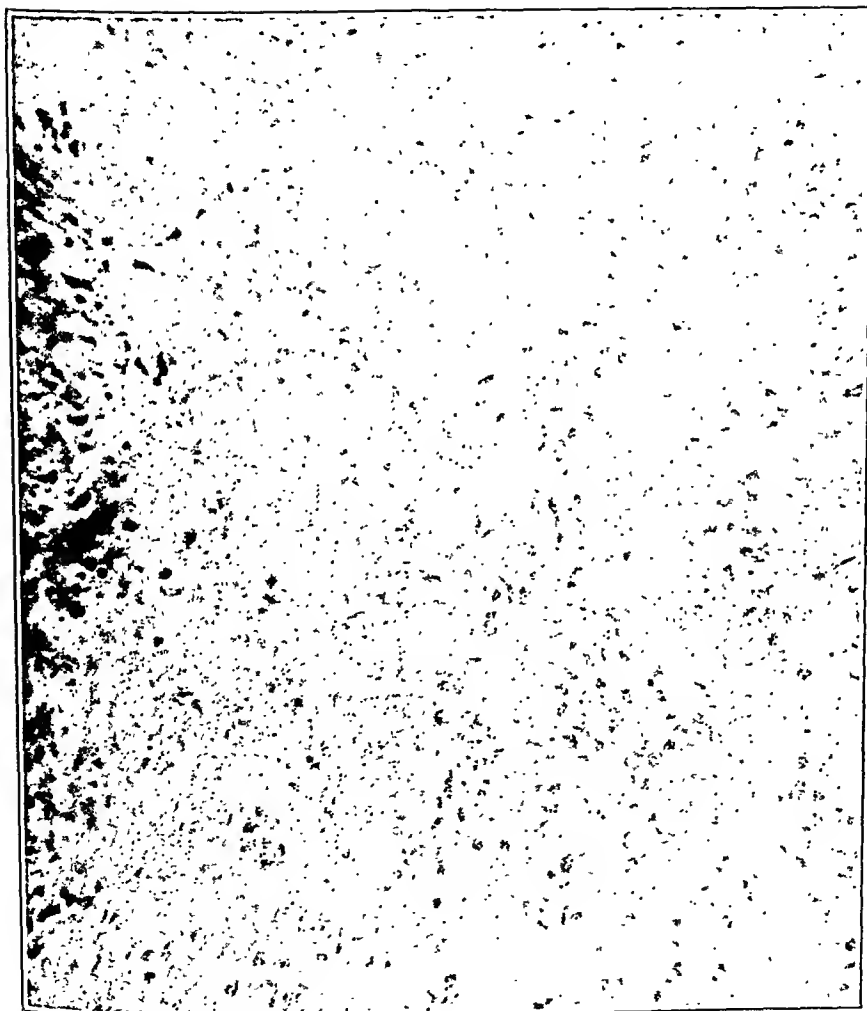


Fig. 3 (case 2).—Tissue from left scapula. Note irregularly shaped cells and giant cells with bone destruction.



for a period of a year and of having noticed shortening of this leg occurring over a period of five years. Furthermore, there was a history of a fall on this side twelve years previously. Roentgenograms revealed generalized Paget's disease. The patient was treated at first with Russell balanced traction, which was not comfortable. She was then placed in a plaster of paris spica. A roentgenogram of the right hip taken three months after her admission may be seen in figure 1C, which reveals marked destruction of the bone in this region, with a large tumor mass. The patient had an extreme amount of pain. Roentgen radiation was used, and later cordotomy was performed to relieve her pain. She died seven months after admission, nineteen months after the onset of severe pain in this leg. The blood levels of

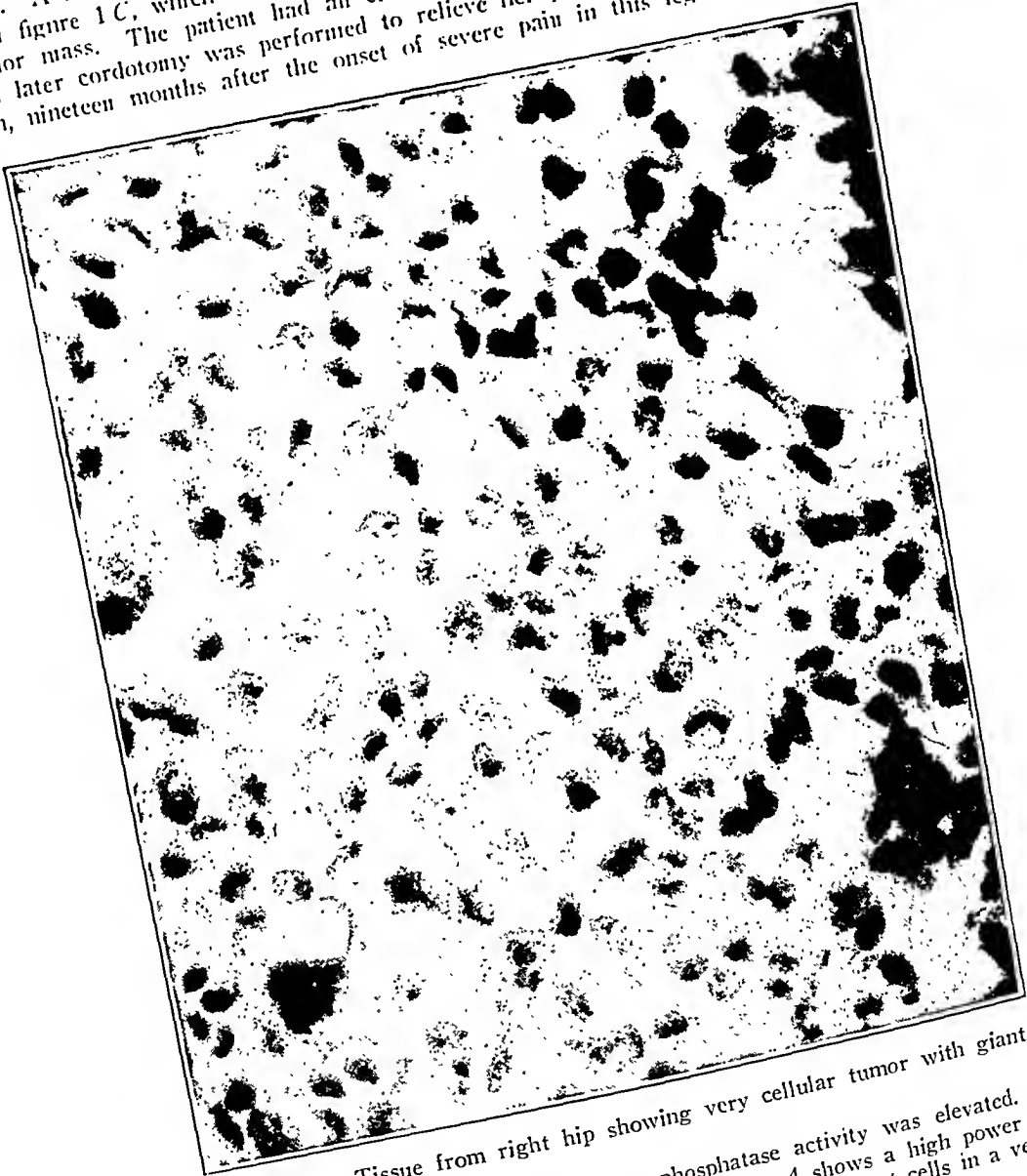


Fig. 4 (case 3).—Tissue from right hip showing very cellular tumor with giant cells. calcium and phosphorus were normal, and the phosphatase activity was elevated. As with the others, there was associated secondary anemia. Figure 4 shows a high power projection of a section of the pathologic specimen of the right hip, revealing giant cells in a very cellular tumor.

#### CONCLUSIONS

Osteogenic sarcoma must be anticipated as a possible complication of Paget's disease of bone in approximately 7 per cent of the cases in a general hospital. The prognosis is universally poor, with a very disagreeable terminal stage.

# INTERNAL BRACE FOR THE LOW PART OF THE BACK

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SAN FRANCISCO

In 1937 I briefly described an original method of surgically bracing the low part of the back.<sup>1</sup> The present article is written to summarize the advances in technic and the results in 53 cases in which this operation was performed in the past twelve years.

## INDICATIONS FOR OPERATION

The type of back to which this operation is suited is one which shows structural instability of the lumbosacroiliac joints, singly or severally. There must not be any signs or symptoms of arthritis or tuberculosis, conditions for which the standard spinal fusion and more prolonged recumbency are indicated. Marked relaxation of the sacroiliac joints, as shown by inclinometric measurements, together with persistent sacroiliac symptoms, is a valid indication for the operation. Another indication is a persistently recurring subluxation of one or more lumbar articulations. The downward subluxations, with or without actual rupture of the intervertebral disks, are especially prone to repeated recurrence which may require internal splinting. I feel that laminectomy for removal of a ruptured intervertebral disk should be accompanied almost invariably by an internal back brace. Finally, almost all types of spondylolysis and spondylolisthesis are best splinted by this type of operation.

## JOINTS THAT MAY BE SPLINTED BY THE INTERNAL BRACE

Starting with my modification of the Verrall tie rod graft, which splints both sacroiliac joints, the brace may be extended upward to include any or all of the lumbar vertebrae.

## TECHNIC OF OPERATION

Given the indications noted, and disregarding all previous trials and errors, one finds that the present technic is well standardized. All subluxations and sacroiliac slips are reduced by manipulation, with or without anesthesia. Thereafter, the patient must be brought to a condition of complete comfort by rest in bed and traction. Comfort cannot always be obtained for patients who show actual impingement on nerve roots, but the more comfortable the patient becomes before operation, the more spectacular is the operative result.

After a two day preparation of the skin of the low part of the back and of both legs, the patient is anesthetized by rectal instillation of a solution of avertin with amylene hydrate and by inhalation of ether. He is placed prone on the operating table with a pillow beneath the pelvis and rolled blankets beneath the shoulders. An intravenous infusion of 5 per cent dextrose in physiologic solution of sodium chloride is started and is allowed to drip slowly throughout the operation. Each thigh is encircled by a blood pressure cuff, and the ground plate of a cautery knife is placed beneath the abdomen. Both legs and the lower part of the back are prepared and draped.

1. Pitkin, H. C.: Sacroarthrogenetic Telalgia: Plan for Treatment. *J. Bone & Joint. Surg.* 19:169-184 (Jan.) 1937.

The operator identifies, by palpation, the spinous processes of the lumbar vertebrae that are to be splinted and starts the midline incision one vertebra above the limits of the brace. The incision is extended caudally to the third sacral spine, which is the one distal to a line connecting the posterior superior spines of the ilia. All bleeding of the skin is controlled by clamp and electrocoagulation. The skin is isolated by laparotomy pads and skin clips. The fat, fascia and muscles are dissected from the tips of all the spinous processes with the electrocautery knife, and the dissection is continued with a periosteal elevator until the laminae and zygapophysial articulations are exposed. If there has been any question of impingement on a nerve root, that root is exposed by lateral laminectomy of the peek hole type and is freed from all pressure.

At this point in the operation the table is broken at the level of the umbilicus to flatten the lumbar spine. With a flexible probe, the operator makes a profile of the exposed laminae from the third sacral upward to the cranial end of the brace. To fit this profile, after the blood pressure cuffs have been inflated, two curved grafts are cut from one tibia with the Cayo saw. Each graft is 12 mm. square at the cranial end and tapers to a point at the caudal end. The transsacral tie rod graft is cut from the other tibia. It is 12 mm. square, and its length is equal to the distance between the sacroiliac joints at the level of the posterior superior iliac spines as measured on the anteroposterior roentgenogram. For convenience, one end of this graft is bluntly pointed, and the other end is cut squarely across. When the tibial wounds have been closed, each leg is wrapped loosely with sheet wadding and Ace bandages from the toes to mid thigh, and the blood pressure cuffs are deflated.

My flat drill guide is now laid across the back at the level of the posterior superior iliac spines and is held in place by the assistant. By measuring from the center of the drill guide anteriorly to the base of the second sacral spine, the operator determines the depth at which the drill holder shall be set. The drill holder is affixed to the end of the drill guide. The drill itself is round, measures 8 mm. in diameter, has a reamer point and, at its base, swells to a recessed butt that is 10 mm. square. The drill is introduced through the drill holder at the predetermined depth into a stab wound in the buttock. By to and fro rotation, so as not to wind up the muscles through which it passes, the drill is forced in turn through the gluteal muscles, the wing of the ileum, the erector spinae muscles, the spine of the second sacral vertebra, and in the reverse order through the structures of the farther side. The drill guide and drill holder are removed, and the sharpened end of the tie rod graft is inserted into the recessed butt of the drill. With a hammer, the graft is driven through, driving the drill before it. Thus, a round hole, 8 mm. in diameter, drilled into cancellous bone, is enlarged to a 10 mm. square by the swollen butt of the drill, and then to a 12 mm. square by the driven tie rod. This insures complete solidity of the tie rod graft.

For uncomplicated cases of sacroiliac relaxation, closure of the midline incision and of the two stab wounds completes the operation. When varying degrees of lumbar instability are encountered, the tie rod functions as a foundation for the longitudinal paraspinous grafts. As already described, these two curved grafts are cut to fit the profile of the laminae from the third sacral vertebra cranially to the required distance. The pointed ends of the longitudinal grafts are inserted between the tie rod and the second sacral laminae, one on each side of the spinous process. With a Smith-Petersen graft impactor and a hammer, the grafts are driven caudally. Because of the posterior inclination of the second and third sacral laminae, the farther the grafts are driven, the more tightly their cranial

ends are approximated to the lumbar laminae. When the previously broken operating table is brought back to level, and the lumbar curve is restored, the entire brace is so tightly impacted that the operator is able to lift the patient's pelvis and lumbar spine as a unit by means of a Kocher clamp applied to any of the three grafts. Finally, the lumbar spinous processes are split longitudinally with a chisel and are turned down bilaterally to form a roof over the paraspinous grafts. It is my present practice to dust each of the wounds with powdered sulfanilamide before closure.

#### POSTOPERATIVE CARE

To avoid the formation of postoperative hematomas, the patient is kept supine for twenty-four hours after operation. After the first day all activity is left entirely to the patient's inclination. In this series, the shortest hospital stay was ten days, the longest was fifty-nine days, and the average was less than twenty-two days. Because of the inherent stability of the internal brace, no form of external support is needed. The surgeon should warn the patient that he may expect a slight loosening of the grafts and a feeling of instability with varying degrees of pain for a few days at about the sixth postoperative week. Thereafter, the grafts tighten up, are replaced by living bone and grow progressively larger for one to two years after implantation.

#### FOLLOW-UP

The longest follow-up in this series is twelve years, and the shortest is six months. With the exception of one operative death, every patient has returned to his usual or an equivalent occupation. In this series, the shortest time for return to the usual occupation or its equivalent was seven weeks, the longest was forty-eight weeks, and the average was less than eighteen weeks. One patient lost her grafts from infection, and although she continues at her usual occupation, she was not helped by the operation. In 3 patients, all women with shallow sacrum, one end of the tie rod broke out of its iliac emplacement when the longitudinal grafts were seated. In 2 of these patients a later operation produced solid union with complete relief of symptoms. The third refused a secondary operation and continues at her usual occupation unrelieved. One rather thin tie rod graft was fractured spirally by muscular effort but healed spontaneously with complete relief of symptoms.

Seventy per cent of the patients in this series had perfect anatomic and functional results. Twenty per cent of the patients were markedly improved but showed some anatomic or functional defect. In 10 per cent the results were classed as anatomic or functional failure. This series represents less than 5 per cent of the patients who were treated for similar conditions in a comparable period, since only those with the most resistant conditions came to operation.

Immediately after operation inclinometric measurements of sacroiliac mobility showed complete immobilization. At the sixth week there is moderate sacroiliac relaxation. By the third or fourth month sacroiliac motion has become and thereafter remains normal. At later operations it has been shown that this motion is allowed by torsion within the tie rod. Similarly, lateral roentgenograms of the longitudinal grafts taken in flexion and extension show no motion at first, then moderate relaxation and finally no motion. It is possible that the longitudinal grafts develop internal torsional movement, as the tie rod does, but it has not been demonstrated.

The roentgenologic follow-up is interesting. All except the 4 most recent patients have been followed for at least one year, and 2 patients have been followed

for twelve years. The dense tibial bone grafts begin to show absorption and replacement by the end of the third or the fourth month. At the end of eight months the grafts seem to have almost the same density as the surrounding bone, and reconstruction of their size and shape is evident. The tie rod now has the appearance of a doubly arched truss that is largest at its three points of bony contact. The longitudinal grafts show bulbous enlargements at all points of contact with the laminae and the tie rod. By the end of the first year replacement and growth are practically complete. In patients who do extremely heavy labor, the grafts have continued to show gradual growth for as long as ten years and appear to follow Wolff's law in response to stress and strain.

#### SUMMARY

An original operation is described which differs from all other types of spinal fusion in the following respects: 1. It immediately immobilizes the desired portion of the low part of the back without any form of external support. 2. It shortens the period of hospitalization to an average of approximately three weeks. 3. It shortens the period of partial disability to an average of approximately eighteen weeks.

Fifty-three patients who were operated on after this method have been followed for from six months to twelve years.

909 Hyde Street.

## AN OPERATION FOR BENIGN CYST OF THE UPPER HUMERAL METAPHYSIS

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A benign cyst (*osteitis fibrosa cystica localisata*) of the upper end of the humeral shaft may be so large that fixation following curettage and packing with bone presents some difficulties, especially when the wall of the cyst is very thin and fracture is present or imminent.

Two such cysts were recently dealt with by me in a manner which I have not seen described heretofore. The method is presented because it seemed to meet the requirements, mechanical and therapeutic, in a satisfactory manner.

In each case (figs. 1 *A* and 2 *A*) the cyst was approached anteriorly, the biceps muscle being reflected medially, the deltoid muscle laterally. The periosteum was carefully reflected medially and laterally to a point about 3 cm. below the distal end of the cyst. A vertical slot was made in the anterior wall of the cyst, exposing the interior, and through this the fluid and the lining membrane were removed.

Two full cortical thickness grafts were removed from the tibia, each being equal in length to the length of the cyst plus about 3 cm. and about 1 cm. wide.

Two transverse slots, one on each side, were then made in the wall of the cyst at the level where the shaft flares out abruptly to meet the humeral head and tuberosities. This level normally is about 4 cm. below the tip of the greater tuberosity; in benign cysts it will vary. Through these slots the two grafts were pushed well up into the interior of the cyst to the latter's proximal limits, toward (but not through) the upper epiphysal plate. The lower portions of the grafts lay outside and snugly against the cortex of the shaft distal to the slots, extending downward to a point about 3 cm. below the cyst.

Two transfixion screws of vitallium or stainless steel were then introduced through transverse drill holes made in the grafts and the normal shaft immediately distal to the cyst. These screws fixed the grafts. The grafts in turn provided stout fixation, in normal relationship, of the epiphysis and the shaft, and at the same time served as bone packing.

In what remained of the cyst chamber were placed a few sizable free bone transplants.

So stout was this fixation in each case that no external splint was necessary. The extremity was suspended from the Balkan frame by the Blake method for one to three weeks, until wound healing was advanced. Both boys were then ambulatory with no other support than an arm sling for eight weeks.

Adequate bony reorganization within the cyst was thought to be established beyond doubt in each case in three months. See figure 1 *B*, *C* and *D* and figure 2 *B* and *C*. When the patient in each case was last seen five months after operation, there was a normal range of motion without pain throughout the extremity, and obliteration of the cyst seemed complete.

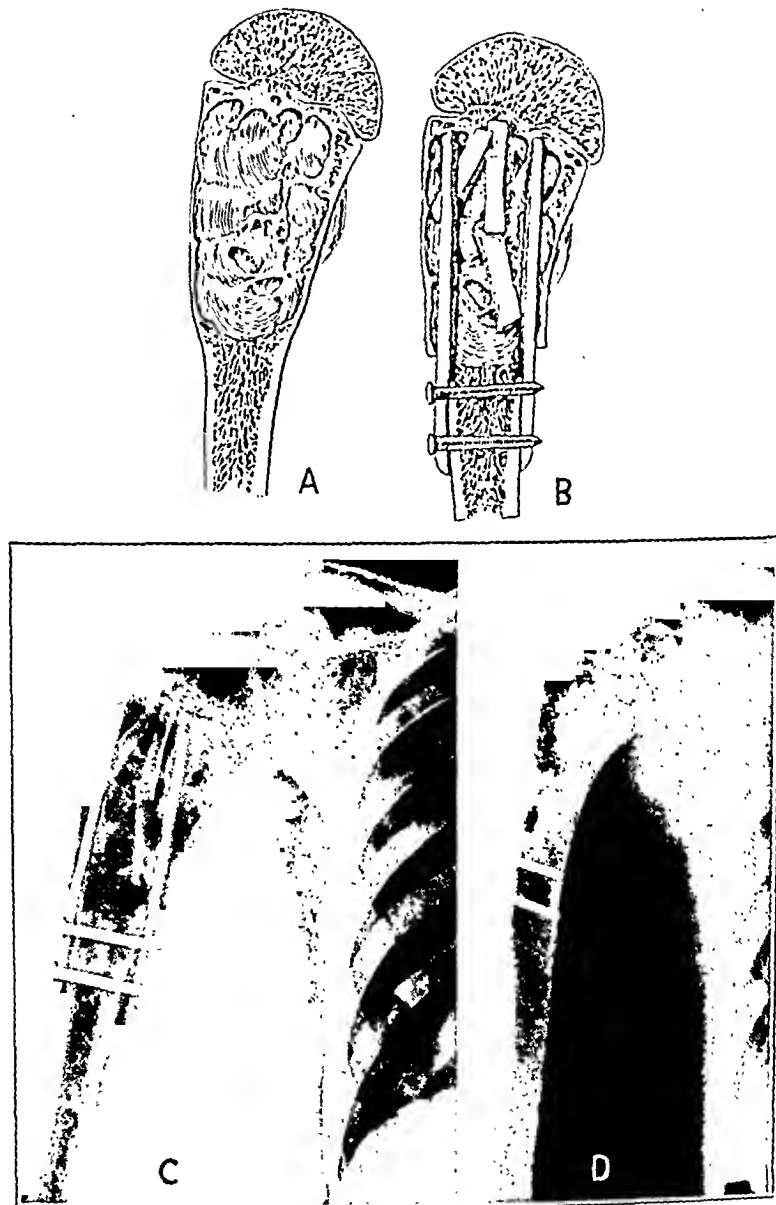


Fig. 1 (case 1).—*A*, artist's drawing of the cyst, made before operation. (The original film has been mislaid; the pathologist's report was bone cyst.) The patient, a boy aged 14, had had three fractures in the past eighteen months. *B*, schematic drawing to illustrate the operative procedure. See text for a detailed description. *C*, roentgenogram made shortly after operation. *D*, roentgenogram made eight months after operation, showing almost complete obliteration of the cyst by bone.



Fig. 2 (case 2).—*A*, osteitis fibrosa cystica. The patient, a boy aged 13, fell, fracturing the humerus through the cyst four days before admission. *B*, roentgenogram taken shortly after operation. One strut was used instead of two. *C*, roentgenogram taken five months after operation, showing almost complete obliteration of the cyst by bone.



# AN OPERATION FOR CORRECTION OF RECURRENT DISLOCATION OF THE JAW

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MILWAUKEE

As a variant to the procedures of either injection of the capsule or removal of the discus articularis for recurrent dislocation of the jaw, I have come to prefer the following procedure as more positive than the first and simpler and more positive than the second.



Fig. 1.—One-inch (2.5 cm.) incision made 1 inch in front of the external meatus of the ear.

A vertical 1-inch (2.5 cm.) incision is made about 1 inch anterior to the external meatus of the ear as shown in figure 1. The skin here tends to form vertical folds. If the closure is skilfully done the scar is hardly discernible. This line will correspond to the anterior border of the condyloid process of the mandible with its upper limit over the tubercle of the zygomatic process of the temporal bone. A speculum retractor (*a* in fig. 2 *A* and *B*) is pushed into the wound along and touching the anterior border of the neck of the mandible until it is stopped by the tuberculum articulare of the temporal bone. Through the speculum a  $\frac{3}{16}$  inch (0.35 cm.) drill (*b* in fig. 2 *A*) is introduced. It will impinge on the tuberculum articulare. The drill is held in the frontal plane and is directed cephalad

at an angle of 45 degrees. The drill is sunk until it pierces the inner table of the temporal bone. The bone is  $\frac{5}{16}$  inch (0.08 cm.) thick here. The drill hole is tapped with tap *c* (fig. 2 *A*). A shoulder bone peg  $\frac{1}{4}$  inch (0.39 cm.) (*d* in fig. 2 *A*) is then screwed into the hole until it breaks off at *e* (fig. 2 *A*), which leaves a bone plug (*f* in fig. 2 *C*) projecting  $\frac{1}{4}$  inch (64 cm.) from the tuberculum articulare as a buffer against which the condyloid process of the

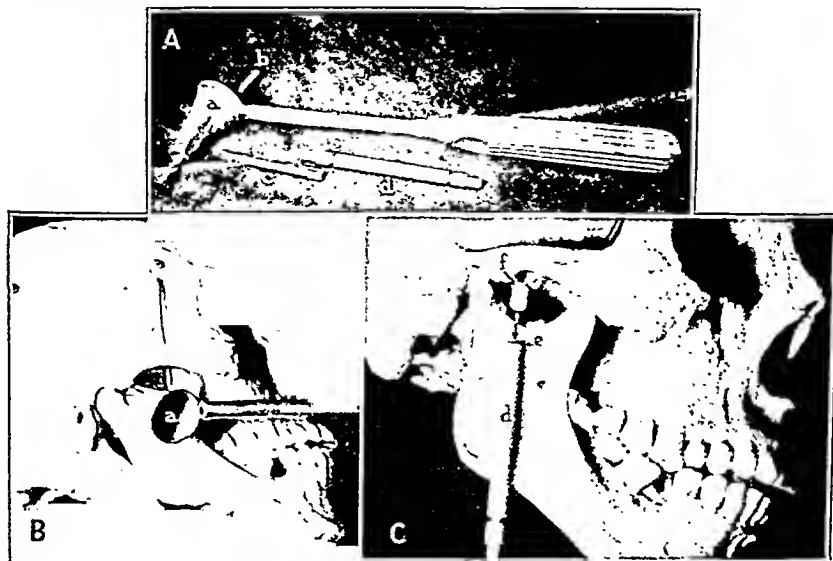


Fig. 2.—*A*, tools used in the operation: (*a*) speculum retractor; (*b*) drill; (*c*) top; (*d*) bone peg; (*e*) breaking point of peg. *B*, insertion of speculum retractor (*a*). *C*, bone plug left after breaking off of bone peg *d* at *e*.

mandible will impinge. On removal of the speculum the wound closes spontaneously. The skin is sutured with horsehair. The scar is negligible.

Effective hemostasis is important. The only complication that has occurred was temporary partial paralysis of the facial nerve, which disappeared with absorption of the hematoma.

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# USEFUL SURGICAL PROCEDURES FOR RHEUMATOID ARTHRITIS INVOLVING JOINTS OF THE UPPER EXTREMITY

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AND

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BOSTON

"Wait until the acute condition quiets down." "Don't operate during the acute stage." These statements express the commonly accepted opinion about surgical procedures undertaken during the active stage of rheumatoid arthritis. The lack of success of fascia lata arthroplasty and of synovectomy when undertaken during the acute stage is the obvious reason for this prevailing opinion. The success of vitallium mold arthroplasty undertaken in spite of active disease has made us stop to analyze the pros and cons of operative treatment.

To relieve pain, to arrest the disease process and to preserve function are the aims of treatment of any acute condition of a joint. "Rest" is the principle of all so-called "conservative" nonoperative measures. As a rule, the "rest" treatment is successful in relieving pain, sooner or later; as a rule, the "rest treatment" is successful in arresting the disease process locally; when it comes to preserving function, the "rest" treatment is generally unsuccessful; this is particularly true since it affects not only the primary joint but also the other joints of the extremity, rendering them more vulnerable to the disease process. If it were possible to put one joint at rest without affecting the other joints of the extremity, the "rest" treatment might be justifiable, but when putting one joint at rest jeopardizes the function of the other joints, the treatment becomes questionable. A joint immobilized or put at rest in a plaster cast becomes less painful because acutely inflamed, congested structures are prevented from performing their function; nature is partially successful in bringing about this same result by its own method of immobilization, that of muscle spasm. Neither method is ideal; both have distinct drawbacks.

Nature's "protective muscle spasm" is the gentlest, mildest form of immobilization; it diminishes pain by diminishing function and by putting the affected joint in a position of minimum discomfort. This position is rarely, if ever, the optimum functional position and consequently must not be allowed to persist for a long enough time to produce a lasting deformity of the joint involved as well as of the other joints of the extremity; one must recognize the fact that as soon as one joint of an extremity is put into a position of deformity, the other joints of that extremity are made to function in a corresponding, proportionate position of deformity. The first objection to immobilization by protective muscle spasm is the position of deformity involving not only the primary joint but also the other joints of the extremity.

Muscle spasm affects the circulation, both arterial and venous; it diminishes the arterial circulation of all the muscles in spasm as well as that of all the structures distal to it; it interferes with the venous return, causing congestion and

edema of all the structures distal to the region of spasm. The second objection to immobilization by muscle spasm is the interference with circulation, diminishing nutrition to other joints and rendering them more vulnerable to disease.

Muscle spasm interferes with the motion between muscles, between muscles and fascia and between muscles and underlying bone; it creates increased tension and friction, resulting in fascitis and bursitis. These conditions in themselves may be productive of greater pain than the condition of the joint primarily affected and thereby delay the return to function. Bursitis and fascitis, then, represent still further objections to immobilization by protective muscle spasm.

Atrophy of muscles, ligamentous loss of elasticity, atrophy of bone represent other complications of immobilization by protective spasm of muscles; they also complicate artificial immobilization by means of plaster casts, braces or other means of partial or complete elimination of function.

Artificial immobilization relieves pain by partial or complete elimination of function; it also attempts to avoid one of the complications of immobilization through spasm of muscles by putting the joint at rest in the optimum functional position. This is not altogether desirable since it subjects the articular surfaces to continuous apposition, one surface being forced against the other by the resistance of the controlling muscles. The effect is distinctly less noticeable in cases of immobilization by traction, but even this form of treatment has some of the unfavorable pressure aspects. Joint surfaces exposed to continuous apposition and pressure, one against the other, instead of the normal intermittent pressure and friction, undergo degenerative changes more quickly than if they were allowed at least partial function. This must be kept in mind and immobilization necessary for the relief of pain made use of for the shortest possible period. Any secondary source of pain must be avoided by eliminating prolonged immobilization.

The active, or muscular, support and the passive, or ligamentous, support of a joint undergo changes characteristic of the tissues of which they are composed when they are deprived of their function. Muscle fibers atrophy in proportion to the length of time that they are forced to remain at rest; such atrophy is accompanied by loss of elasticity on the part of the fibrous tissue framework. These changes represent distinct obstacles to restoration of function. The passive supporting ligaments normally have a certain amount of elasticity, but it is slight in comparison with the muscular elasticity. When they are deprived of their function, their elasticity is diminished and they become structures very resistant to restoration of motion in the joint which they support.

Atrophy of bone represents the final objection to prolonged immobilization. Whether or not such atrophy is a source of pain, we are unable to say, but that is a possibility. There can be no question, however, that it renders surgical restoration of function more difficult. Keeping in mind that a joint represents the fulcrum through which the controlling muscles exert their leverage, it is clear that postoperative exercises, aiming to restore muscle power and overcome inelasticity, will tend to force the newly created joint surfaces against one another; in the presence of atrophy of bone such postoperative treatment will tend to distort the potential joint, which consequently will have a diminished range of motion.

We have presented some of the main objections to conservative treatment by immobilization. We do not mean to imply that immobilization is never indicated: it is indicated for relief of pain but should never be carried to a point where it creates obstacles to successful surgical treatment. One must constantly be on guard against carrying the treatment to a point productive of secondary sources

of pain, such as bursitis and fascitis. If such secondary conditions do arise, they must be eliminated, so that the functional treatment of the primary condition can be undertaken at the earliest possible moment.

Functional treatment, aiming to relieve pain by medication, is distinctly more desirable, but even such treatment can be carried to a point creating conditions difficult for the surgeon to overcome. The internist and the surgeon are apt to wait for the roentgenograms to show advanced destructive changes before resorting to operative treatment. It is only in retrospect, when they see local deformity, as well as deformity of other joints secondarily involved, that they say, "We should have operated at an earlier stage and thereby prevented these deformities; now we have to correct them."

Rheumatoid arthritis involving any one of the joints of the upper extremity brings on protective muscle spasm producing a position of deformity which is essentially the same, no matter which joint is involved. The position of deformity of the shoulder is one of adduction and internal rotation; that of the elbow is one of flexion accompanied by diminution of motion in pronation as well as in supination; that of the wrist is one of diminished dorsiflexion accompanied by ulnar deviation. Limitation of pronation and supination at the wrist is, of course, dependent on limitation of these same motions at the elbow and vice versa. The small joints of the hand gravitate in the direction of ulnar deviation and flexion. Since one painful joint is apt to result in limitation of motion of all the other joints, with all the evils that accompany such limitation, it is important to mobilize the joint primarily involved as soon as possible and not delay the return of function of the joints secondarily involved any longer than absolutely necessary. With this in mind one must continually be on the lookout for a change in the pain or discomfort produced by the primary lesion. The shoulder joint is a good example of what we mean by this statement. Rheumatoid arthritis involving the glenohumeral joint results in a position of adduction and internal rotation of that joint. The muscle spasm producing this position affects not only the joint itself but also the subacromial and subdeltoid bursas, and these structures become involved early in the inflammatory process. Since scapulothoracic motion to a considerable extent depends on locking of the glenohumeral joint, and since locking of the glenohumeral joint produces increased tension of the subacromial bursa, an acute inflammatory condition of the subacromial bursa automatically eliminates scapulothoracic motion. In other words, subacromial bursitis accompanying rheumatoid arthritis of the glenohumeral joint practically eliminates function of the shoulder and secondarily of the entire upper extremity. In order to restore function, the pain arising from the subacromial bursitis must be eliminated; we have found the operation of acromioplasty a satisfactory procedure for this purpose. By excision of the acromion the central tendon of the deltoid muscle is brought into apposition to the scapulohumeral tendinous cuff and it is this relationship which brings about relief from pain and allows the patient to make use of whatever motion there is in the scapulohumeral joint and to compensate for the diminished motion in the scapulothoracic motion.

#### ACROMIOPLASTY

The first operation of acromioplasty was performed in September 1935 for the relief of pain arising from the impinging of an exostosis of the anatomic neck of the humerus on the acromion. Excision of the acromion enabled the patient to make use of her scapulothoracic motion and improved the glenohumeral motion also, although not markedly. The striking effect was the improvement in function

of the entire upper extremity because of the elimination of pain. This is now seven and a half years ago and the patient has remained comfortable and able to use her upper extremity for practically all routine activities. Since that time the operation has been performed on 11 patients, all with rheumatoid arthritis—unilaterally in 8, bilaterally in 3. The results have been satisfactory in practically all the cases. When we say "satisfactory," we refer particularly to the relief from pain; there has not been any striking increase in the range of motion in the glenohumeral joint. The improvement in function has in all cases been due to improvement in compensatory scapulothoracic motion. These 11 cases were all instances of rheumatoid arthritis, and the operation was not undertaken in a single instance until there were advanced changes in the glenohumeral joint. Since the operation is not a destructive procedure, it seems reasonable to suggest that it be undertaken as soon as the diagnosis of subacromial bursitis is made, even though the roentgenograms do not show an advanced destructive process in the glenohumeral joint. We are confident that if the operation is undertaken early, even better functional results may be obtained.

*Operative Technic.*—Various incisions have been used. The S-shaped or bayonet incision has been found the most practical; it starts at a point  $\frac{3}{4}$  inch (2 cm.) anterior to the anterior angle of the acromion and extends to a point  $\frac{3}{4}$  inch posterior to the posterior angle of the acromion. The insertion of the trapezius muscle is defined from the origin of the deltoid muscle and the periosteum between these muscle attachments incised. The deltoid muscle is reflected from a point just lateral to the acromioclavicular joint to a point just mesial to the posterior angle of the acromion. By this reflection of the deltoid muscle the subacromial bursa is exposed. A tape or a small sponge is passed under the acromion and the acromion excised by means of an osteotome. The acromioclavicular joint should be left intact; the posterior angle of the acromion should be included in the excision. The subacromial bursa, now completely exposed, is commonly found filled with congested villi covering the underlying tendinous cuff. As complete a synovectomy as is indicated by the findings should be carried out.

There is one important point to be observed in the closure of the wound; that is the careful approximation of the central tendon of the deltoid muscle to the periosteal attachment of the trapezius muscle. By reflecting the periosteum to which the trapezius muscle is attached, i. e., from the acromioclavicular joint to the spine of the scapula, a better approximation is achieved.

This operative procedure aims to relieve pain arising from the secondary lesion, that of subacromial bursitis. On eliminating this source of pain better function can be expected on the part of the joint involved primarily, i. e., the glenohumeral joint, as well as improvement in compensatory motion between the scapula and the thorax.

#### EXCISION OF THE HEAD OF THE RADIUS

Rheumatoid arthritis involving the elbow joint results in limitation of flexion and extension as well as pronation and supination. The radial head plays an important part in all motions of the elbow; consequently if one can eliminate pain associated with function on the part of that structure, one can expect a distinct improvement in the function of the elbow joint as a whole. The biceps muscle is the one involved in protective muscle spasm to a greater extent than any other muscle; because of the spasm of this muscle, extension and pronation are affected early in the disease process. At operation we have repeatedly observed a discrepancy in alignment between the radial head and the capitellum; we have found

the radial head lifted upward in such a way as to prevent it from moving in a correct mechanical fashion over the congruous surface of the capitellum. We have found in the articular surface of the capitellum a sulcus or a depression corresponding to the inferior articular margin of the radius. This joint defect is comparable to the joint defect in the femoral condyle produced by the articular margin of the tibia in spasm of the hamstring muscles.

The natural answer to the mechanical interference with flexion and extension as well as pronation and supination is excision of the radial head. There is no need of dwelling on the details of this procedure since it is a generally accepted operation for relief of any condition interfering with normal function between the radius and the ulna or the radius and the capitellum. The operative findings have been instructive since they have been decidedly comparable to the changes in the subacromial bursa in rheumatoid arthritis. Synovial villi frequently herniate through the incision into the articular capsule; they arise from the synovia and are eliminated during the second stage of the operation, that of partial synovectomy. The villus formation may at times be so extensive as to make desirable extending the synovectomy to the pouch of the triceps muscle; this can be done by reflecting muscular attachments posteriorly from the epicondylar ridge. The objection may be raised that since this operation consists not only in excision of the radial head but also in a rather extensive synovectomy, the beneficial results may be accounted for on the basis of the synovectomy rather than on the basis of the excision of the radial head. When we first undertook this operation, the synovectomy was decidedly incidental, but even so good results were obtained. In cases in which the more extensive synovectomy seems indicated, there can be no question that this part of the procedure is distinctly helpful; it would not be constructive, however, if undertaken without the excision of the radial head—as a matter of fact, it would not be technically possible.

Excision of the radial head has been performed in 10 patients, in 5 bilaterally and in 5 unilaterally. Again the results have been striking as far as relief of pain is concerned. The motion in flexion and extension has not been markedly improved, but it has been benefited; the outstanding benefit has been the improvement in pronation. We have no patients sorry that the operation was performed; they are all grateful for the relief it has afforded.

Again it seems right to point out that the earlier this operation is performed, the better the functional result. In our series the operation has not been performed until the roentgenograms showed advanced destructive changes involving all the joint surfaces.

#### ARTHRODESIS OF THE WRIST; EXCISION OF THE DISTAL END OF THE ULNA

In 1936 William Darrach<sup>1</sup> published an article on excision of the distal end of the ulna for relief of pain arising from faulty mechanics of the wrist secondary to fractures of that region. Based on this article, a new approach to the wrist joint was developed.<sup>2</sup> Arthrodesis performed through this approach has been particularly satisfactory because of the excision of the distal end of the ulna; this preserved whatever motion there was in pronation and supination and in some

1. Darrach, W., in *Libre jubilaire offert au docteur Albin Lambotte par ses amis et ses élèves*, Brussels, 1936.

2. Smith-Petersen, M. N.: A New Approach to the Wrist, *J. Bone & Joint Surg.* 22:122-124 (Jan.) 1940.

cases improved the range of motion. The dorsal approach to the wrist is very satisfactory and excellent results are obtained as far as fusion of the radiocarpal joint is concerned, but, since the ulna is left intact, motion in pronation and supination does not benefit. When one has a disease process to deal with, as one has in rheumatoid arthritis, it is particularly important to eliminate pain arising from the radioulnar joint, and this can be accomplished only by excision of the distal end of the ulna.

Arthrodesis has been done through this approach in 5 cases, with relief from pain and preservation of motion in pronation and supination. In 4 cases the distal end of the ulna was resected without fusion of the radiocarpal joint, since this joint was not involved to such an extent that fusion seemed justifiable. It does not seem fair to pass judgment on an operative procedure on the basis of 4 cases only: it is our impression that the patients who had excision of the distal end of the ulna plus arthrodesis of the radiocarpal joint have done better than the patients who had excision of the distal end of the ulna alone.

#### METACARPOPHALANGEAL AND INTERPHALANGEAL JOINTS

The metacarpophalangeal and interphalangeal joints may be involved in the disease process of rheumatoid arthritis primarily, or they may become involved secondarily to disease of one of the major joints of the extremity; in either case disalignment, flexion, subluxation and ulnar deviation occur relatively early. We say "relatively early" because we are unable to give a definite estimate of the time element, but we are anxious to emphasize the danger of the joints becoming involved from the very first. Obviously, the reason for this threat to the function of the hand is the force of gravity. The minute any joint of the upper extremity is involved in a disease process protective muscle spasm puts it in a position demanding defense against the deforming force of gravity. Since the force of gravity is active continuously but the defense is not, deformity is the result—a deformity which is difficult, sometimes impossible, to correct. The natural conclusion is that no pathologic condition of a joint must be allowed to persist for a time long enough to give gravity a chance. If operation is undertaken early, eliminating pain arising from one of the major joints of the upper extremity, the smaller joints will continue to function and thereby be able to survive without being destroyed by the disease process. We cannot prove that this is so; we submit it for consideration and analysis, along with suggestions made for early operative treatment of the larger joints of the upper extremity.

#### SUMMARY

Reasons have been advanced for undertaking early operative treatment of rheumatoid arthritis in spite of active disease. Early operative treatment is urged in order to prevent the rise of secondary sources of pain. We urge conscientious analysis of pain complained of so that surgical treatment can be undertaken if the character of the pain changes, since this may be indicative of what we choose to call secondary sources of pain. If there is evidence of bursitis or fascitis, the advisability of surgical treatment of so-called secondary sources of pain must be seriously considered. The point that we are most anxious to bring home is early surgical treatment before destruction of the joint is too far advanced to allow maximum benefit from the operation.



The operative procedures suggested—acromioplasty, excision of the head of the radius and excision of the distal end of the ulna, with or without arthrodesis of the wrist—are constructive procedures. It is hardly fair to call them minor, since that will immediately bring about a diminished respect for them. Let us refer to them as being constructive procedures for use before the disease process is far advanced. We feel justified in recommending them because they have given satisfaction to the patients and to the surgeon. The surgeon has been satisfied because of the relief of pain in spite of the fact that the range of motion has in no case been strikingly improved.

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## POSITIONAL PAIN

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Pain arising from bodily positions must be distinguished from postural discomfort. Posture, physiologically speaking, is the *active* maintenance of an animal's station in its environment. It is a manifestation of muscular activity sustained largely by proprioceptive reflexes in accordance with inherited nervous patterns, modified by social customs and personal approbations or taboos. It connotes resistance to external forces, such as air currents and gravity. Position, on the other hand, is imposed on a part, and the station is maintained by *passive* factors. It connotes relaxation and rest. In bed, when one puts one's hands over one's head the arms lie inertly on the pillow. They have position, not posture, because they are not muscularly active but at rest.

Pain may arise from the position imposed on a part if the position is long or frequently maintained. For example, there may be pain in the region of the internal lateral ligament of the knee without any other clinical manifestations. Such pain I have found is associated with the frequent curling of the toes around the legs of a chair from within out. The thigh and toes are supported; the heel is free, and the weight of the leg draws it into extreme external rotation and abduction. The chief sustaining structure is the internal lateral ligament of the knee. How frequently or how long this position must be maintained before pain develops I am unable to say. However, once such pain has occurred the person may be free from it a good share of the time as he moves around, only to have it appear a few minutes after he has seated himself and assumed his favorite position. The pain may be quickly relieved by placing the feet forward, or wrapping them around the chair leg the other way.

Discomfort may come while a person is lying in bed on his face. I have observed the development of pain in the shoulders severe enough to wake one up when the forearms are placed under the forehead or above the head while sleeping. The pain occurs in the anterior part of the shoulder in the region of the bicipital groove. It is almost instantaneously relieved by placing the hands under the thighs.

A third form of positional pain arises when a person is in the prone position and one thigh is drawn up into abduction. The pelvis is raised on that side and the trunk tends to be flat; the result is a localized painful strain on the elevated side of the lumbosacral junction. This is quickly relieved by straightening the thigh.

It would seem, therefore, that the pain arises from a chronic strain of ligaments or tendons not ordinarily subjected to long-continued strains.

These brief observations may seem of little moment, but such pain is baffling to one who has been taught to seek only after the hard things. It is annoying to the patient and hard on the physician's reputation if he does not find the cause.

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# THE TELESCOPING V OSTEOTOMY

## A GENERAL METHOD FOR CORRECTING ANGULAR AND ROTATIONAL DISALIGNMENTS

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Stable impingement of fracture fragments often occurs spontaneously. Maintenance of position is seldom a problem, and union is usually prompt. This principle of stable apposition has been generally applied in the treatment of fractures. In most cases the surgeon strives for such apposition in performing osteotomy.

The pointed telescoping type of osteotomy is not new, but I feel that the principle of inherent stability deserves a more general application through the simple method of this type of osteotomy than is often observed. While most surgeons have utilized the principle, the method receives scant attention (Steindler<sup>1</sup>; Campbell<sup>2</sup>). When the principle is properly applied, slight but precise corrections are easily maintained, and great modification of alignment may be attained without resort to a complicated procedure or to metallic fixation.

Up to late in the nineteenth century osteoclasis was the only safe means of correcting deformities of the long bones. During the twentieth century roentgenograms and open osteotomy have provided such an opportunity for precise planning and meticulous execution that the restricted field of osteoclasis has been replaced by the virtually unlimited field of osteotomy. Bony deformities of all ages have been the seat of almost every conceivable type, pattern and complexity of osteotomy.

### TYPES OF OSTEOTOMY

The basic types of osteotomy follow the types of fractures of the long bones. Thus, the osteotomy may be transverse, oblique, curvilinear, longitudinal or stepped. The ends of the cut bone may be smooth or irregularly pointed, comminuted or splintered.

A wedge effect is obtained with a transverse osteotomy at the site of angulation if impingement of the outer cortices results in a hinge action with opening of the concavity of the deformity on straightening the bone. This also slightly lengthens the bone. Apposition is consequently limited, the position is not secure and the method is applicable to relatively minor deformities. The fragments tend to readjust themselves to secure more stable apposition, with loss of correction, or sometimes slip entirely, with overriding. This situation was so obvious that the origin of cuneiform osteotomy probably goes back at least to the time of Macewen.<sup>3</sup>

Wedge or cuneiform osteotomy may be readily adapted to the large majority of angular deformities of the long bones. The shape, size and location of the wedge can be anticipated with geometric accuracy by means of roentgenograms. Occa-

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This article is based on a preliminary report read at the meeting of the Western Orthopedic Association, Seattle, July 30, 1937.

1. Steindler, A.: *Orthopedic Operations*, Springfield Ill., Charles C Thomas, Publisher, 1940.

2. Campbell, W. C.: *Operative Orthopedics*, St. Louis, C. V. Mosby Company, 1939.

3. Macewen, W.: *Clinical Lecture on Antiseptic Osteotomy*, *Lancet* 1:449, 1878: cited by Steindler.<sup>1</sup>

sionally the site of the wedge is slow to unite. If the wedge is cleanly removed, two relatively plane surfaces are left, leaving a problem of maintenance that has not always been solved, especially in the adult. This has led to utilization of various means of internal fixation, and more recently, as in Pauwels' <sup>4</sup> reinclination operation (Schanz operation), to the use of transfixation spikes extending out of the wound for fixation in the plaster cast.

The easier problem of maintenance encountered when fracture fragments present relatively transverse but irregular surfaces has naturally led to stimulation of that advantage in osteotomy. This is seen to an advanced degree in the longitudinal or splintering osteotomy of Haas.<sup>5</sup>

The difficulties presented by mature bones with a tendency to break, splinter and displace have led to the application of suitable technics. The curvilinear, stepped and flanged osteotomies, with or without removal of a wedge and sometimes with the use of multiple drill holes to avoid splintering, have had their widest application at the knee and the trochanteric region of the hip. These types have been variously employed, as to previous technic, by different men for many years.

The problem of adequate correction and maintenance of good apposition has been further met by the development of the incomplete osteotomy, the surgeon trusting to an adequate hinge effect on the outer side of the angulation. This principle is limited in its application to the young patient and to sites where the cortex is sufficiently thin to bend rather than break.

A method of osteotomy more generally applicable is that of the oblique or pointed type, the surgeon electing to shape the bone fragments so that one end may impinge onto or into the other.

The soundness of this principle has been well tested. From time immemorial those who set broken bones have endeavored to fix one irregularity into the other. This principle has been invoked in bone grafting, as witness the intramedullary peg, fishtail and combined intramedullary and inlay grafts. It has been advocated for securing maintenance without internal fixation in the open reduction of fractures. It has often been spontaneously at work with a fracture, at osteoclasia and in incomplete fracture or osteotomy. It has been purposely utilized in the various types of subtrochanteric osteotomy at the hip, as recorded by Schumm<sup>6</sup> (though with transfixion pins) and others.

The technic of Klapp,<sup>7</sup> applied at a level where the shaft is of uniform diameter and the bone is wholly cortical, utilizes this principle, though it is difficult to form a socket for the pointed fragment without undue splintering.

One method of correcting hammer toe deformity includes resection of the joint and insertion of the pointed shaft of the proximal phalanx into the larger base of the middle phalanx (Young<sup>8</sup>; Higgs<sup>9</sup>).

#### BONE REPAIR

While there is little precise information as to the biophysical mechanism of bone repair, the anatomic factors underlying it are well understood. Given a frac-

4. Pauwel, F.: Pauwel's Subtrochanteric Wedge Osteotomy in Treatment of Pseudarthrosis of Neck: Case (J. H. Sickmann), *Deutsche Ztschr. f. Chir.* **229**:336-342, 1930.

5. Haas, S. L.: Longitudinal Osteotomy, *J. A. M. A.* **92**:1656-1658 (May 18) 1929.

6. Schumm, H. C.: The Schanz Osteotomy for Fractures of the Neck of the Femur, *J. Bone & Joint Surg.* **19**:955-963, 1937.

7. Klapp, R.: Demonstrationen aus der praktischen Chirurgie . . . Anspitzende Osteotomie, *Arch. f. klin. Chir.* **177**:688-694, 1933.

8. Young, C. S.: Operation for Correction of Hammer-Toe and Claw-Toe, *J. Bone & Joint Surg.* **20**:715-719, 1938.

9. Higgs, S. L.: "Hammer-Toe," *M. Press* **131**:473-475, 1931.

ture of bone or an osteotomy with largely viable fragments lying in close apposition to one another and surrounded by a periosteal envelope, and maintained there, prompt bony union is almost inevitable.

Since an osteotomy is an elective procedure, the surgeon may well require that it conform to these basic principles.

#### THE TELESCOPING V OSTEOTOMY

The method of the telescoping pointed or V osteotomy is applicable to the correction of deformities and conditions necessitating realinement of a bone at a level where the bone is conoidal as seen in longitudinal section. The diaphysial-

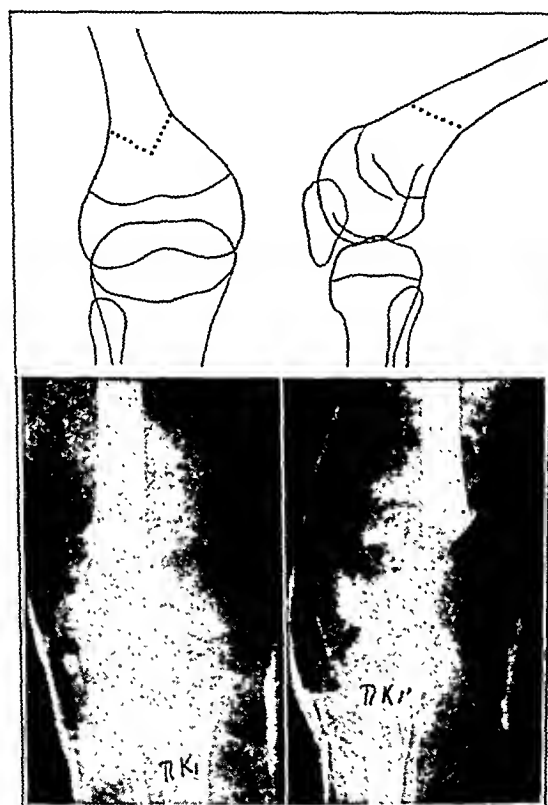


Fig. 1.—The tracings show the valgus type flexed knee of an externally rotated flail leg. The dotted line indicates the proposed osteotomy.

The roentgenograms show the pointed fragment of the shaft telescoped into the metaphysis, correcting the disalignments. Unless epiphysial fusion is present or imminent, deformity from further growth may occur.

metaphysial junction and the metaphysial region of most of the long bones provide this basic requirement. Some diaphysial malunions are also suitable.

The bone is exposed subperiosteally for a short distance on the outer side of the angulation. A V osteotomy is performed, the apex pointing toward the metaphysis and the plane of the osteotomy passing somewhat obliquely away from the metaphysis. In the young person the bone may be incompletely cut, the inner cortex acting as a hinge (fig. 1). Where the cortex on the inner side of the osteotomy is thick, it is better to section the bone completely, to avoid a spiral fracture, or leave but a small section to be broken when the deformity is corrected (fig. 5).

The pointed side of the osteotomy is smaller and more cortical in structure than the metaphyseal receptor side. With slight beveling, the pointed fragment telescopes within the larger. Marked degrees of deformity require, as does rather dense cancellous bone, that the receptor side be somewhat excavated to receive the V point deeply enough to make the telescoping adequate for correction and positive fixation (fig. 2). If the beveling is insufficient, relatively small wedges require removal to avoid impingement of the cortices and consequent loss of apposition and locking. This is important in correcting extreme deformities, when occasionally shortening may be necessary to avoid undue tension on major nerves



Fig. 2.—The two roentgenograms to the left show an adult surgically fused postparalytic knee that, through growth disturbance, had undergone flexion and external rotation. The two postoperative lateral views were taken one day and forty-three days after correction. The tracings indicate the proposed osteotomy by dotted lines. The telescoped end is shown by a broken line.

and blood vessels. Usually, as measured on the inside of the angular deformity, little or no actual shortening occurs.

Thirty years ago, Osgood<sup>10</sup> resected a quadrilateral wedge with the geometric accuracy afforded by roentgen studies and a cardboard model (fig. 3). He shaped the larger distal fragment so that it would retain the smaller when in the corrected position. He noted especially the precision of the correction, its secure maintenance and the early firmness of union.

10. Osgood, R. B.: A Method of Osteotomy of the Lower End of the Femur in Cases of Permanent Flexion of the Knee Joint, *Am. J. Orthop. Surg.* 11:336-346, 1913.

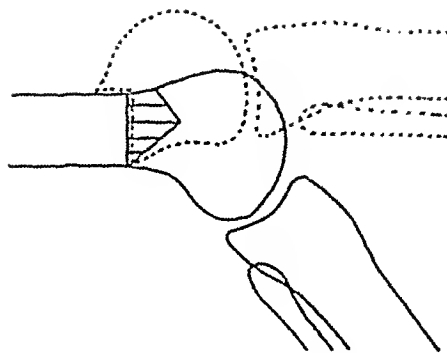


Fig. 3.—Diagram redrawn from Osgood.<sup>10</sup> The permanently flexed knee is shown by solid lines. The shaded area is the quadrilateral wedge, which when removed permits correction as indicated by the broken outline.



Fig. 4.—Old tuberculous hip disease with severe flexion-adduction-internal rotation deformity. Photographs: left, preoperative; right, five years postoperative. Roentgenograms: left, preoperative; right, three months postoperative, taken when the patient began weight-bearing in a short spica. Tracings: left, preoperative. The pointed osteotomy site is shown by a dotted line; the shaded area represents the anterior quadrilateral wedge. Right, postoperative. The broken line indicates the telescoped portion of the distal fragment.

While telescoping of the pointed end of the V osteotomy usually makes resection of cortical bone unnecessary, extreme deformity with scarring of soft tissue may be treated by quadrilateral resection and telescoping to secure stability in all directions.

Such application of the principle was made in the case of a 37 year old woman who had suffered from tuberculosis of the hip from the age of 3, with development of a severe flexion-adduction-internal rotation deformity (fig. 4). A quadrilateral



Fig. 5.—Adducted, probably tuberculous hip of a 31 year old white man. Roentgenograms from left to right: (1) preoperative; (2) postoperative, taken with the hip in a cast (operation March 2, 1937); (3) lateral view of March 9, 1937, with site of osteotomy scarcely discernible; (4) anteroposterior view three months after operation. The vertical line of the view is parallel to the midline of the body.



Fig. 6.—Nonunion of a fractured femoral neck with a viable head. The views from left to right are preoperative and two and one-half months postoperative. The point of the V cut bone is seen telescoped within the intertrochanteric bone. The head is in valgus position. The greater trochanter is below the acetabular margin.

wedge was removed anteriorly and the posterior cortex was bent back to overlap greatly the distal fragment. The hip joint was bone grafted at the same time with the anterior portion of the ilium. Union was prompt, although a tuberculous abscess was encountered.

Whether for slight or marked correction, this procedure closely simulates the impacted (or "telescoping") metaphysal fracture in which apposition and



union are often so firm and prompt as to discourage the surgeon from trying to modify the position a week or so later.

Rotational realignment is obtained by rotating the pointed fragment into line and forcing it into the receptor fragment, a socket having been gouged out if the cancellous bone is too dense or the surface is so large as to prevent sufficient telescoping. The deformities illustrated in figures 1, 2, 4, 6 and 7 presented rotational as well as angular elements.

The shortening as measured on the concavity of the deformity arising from the telescoping is identical with that of the typical cuneiform osteotomy, though occasionally there is slight lengthening as the inner side opens up when the telescoping fragments are firmly seated. Figure 5 illustrates slight lengthening on the inner side. This adducted tuberculous hip was bone grafted at the time of osteotomy. Stable union was remarkably rapid even for this favorable site.

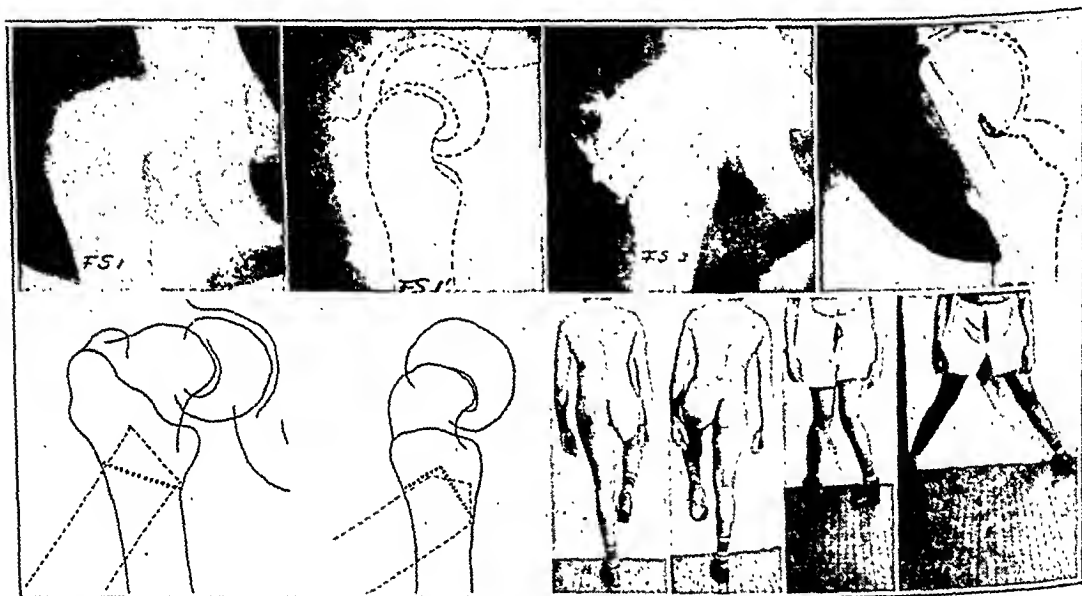


Fig. 7.—Slipped femoral epiphysis in a Negro boy of 14.  
Roentgenograms: left, preoperative; right, four months postoperative.  
Tracings: dots indicate the proposed osteotomy; broken lines, the desired position.  
Photographs: patient one and one-half years later.

It should be noted that even with marked deformities there is little or no shortening as measured by the length of the bone on the concavity or inner angle of the deformity. It is axiomatic that the greater the angular deformity the greater the gain in functional length on correction of the deformity.

More difficult to correct and maintain in correction is a femoral head that has become displaced (rotated) because of nonunion of a fractured femoral neck or because of slipping of a femoral epiphysis. In both instances the head is rotated backward and downward resulting in coxa vara and external rotation.

Figure 6 presents nonunion of a fractured femoral neck with varus deformity and external rotation. Note the obliquity of the fracture plane to the weight-bearing line. After osteotomy a position of complete valgus is obtained, the marked external rotation is corrected and the weight-bearing line meets the fracture plane at nearly a right angle. The apex of the V osteotomy was made posterolaterally, the shaft freed and rotated forward 60 degrees and forced posteromedially into the intertrochanteric region so as to cause adduction and extension of the proximal

fragment, the distal shaft remaining in neutral position. A plaster cast was used for fixation. Union at the site of the osteotomy and at that of the fracture of the femoral neck was prompt.

A marked coxa vara due to slipping of the femoral epiphysis presents a similar problem.

Figure 7 shows a precisely similar correction save for a nail driven across the epiphysial line. A wire loop was used to connect the nail and the distal fragment from osteotomy since 60 degree antiversion angulation was obtained and the operator's confidence in the procedure was not equal to the occasion. It is not now believed that the wiring was necessary. The photographs show the abduction and internal rotation gained. There is no limp.

#### SUMMARY

A method is described for performing osteotomy to correct deformities in which the bone is conoidal in longitudinal section. By a pointed or V osteotomy the smaller fragment may be partially telescoped into the larger to obtain any desired wedge effect or rotational correction. Because of the firm apposition of the partially telescoped living bone fragments enveloped by periosteum, stability is marked and union prompt. No special instruments are required. Plaster casts are used for maintenance. This method of performing osteotomy has been used in diverse situations with good results. While rather marked deformities are shown, the method is no less simple and secure with the mild ones.

Major Francis McKeever, Medical Corps, Army of the United States, gave me permission to use the case shown in figure 1.

2007 Wilshire Boulevard.

## PARATROOPER FRACTURE

CAPTAIN WILLIAM J. TOBIN

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Every now and then there appears in the literature a name associated with a definite type of fracture because of the latter's frequent occurrence in a certain type of injury. Among these are the "crank" fracture of the lower end of the forearm due to the "back kick" of the crank, the "bumper" fracture of the upper end of the tibia and the "dashboard" fracture of the acetabulum.

In two years' observation of the fractures occurring among the parachute jumpers or "paratroopers" in training at Fort Benning, Ga., it has been noted that a substantial number of the jumpers sustain fracture of the posterior articular margin or "posterior lip" of the tibia (fig. 1). Fracture of this type occurring alone constitutes about 12 per cent of the total number of fractures (272). At least another 4 per cent consist of fracture of the posterior lip of the tibia associated with fracture of the internal or the external malleolus. At times the fracture of the posterior lip of the tibia occurs with bimalleolar fracture—forming the trimalleolar fracture of the ankle joint (fig. 2).

In civilian practice it is believed that fracture of the posterior lip of the tibia is relatively uncommon. The usual history in civilian life is that the patient was "tripped" by the heel of the shoe being caught on a step or on a curbing with the foot in equinus position and the weight of the body thrust forward. As the average civilian shoe is a "low quarter" shoe, there is little or no support to the posterior structures of the ankle joint, and when this fracture occurs, open reduction is sometimes necessary to bring about reapproximation of the fragments. While the fracture occurs much more frequently in paratroopers than in civilians, it is not severe.

There has been no case in the series studied that required an open reduction. Undoubtedly, the high tight-fitting boot worn by the jumpers explains this. The astragalus is not pushed backward to any appreciable degree, and consequently the integrity of the posterior ligamentous structures, while stretched and undoubtedly partially torn, are not completely separated. Naturally, if the causative force is sufficiently great, as in a few cases, there does occur a posterior dislocation of the ankle joint.

Another interesting observation has been that the jumpers often "reach for the ground" when they are about 20 feet (6 meters) from it. As a result, the foot is in plantar flexion. It is a popular misconception that the parachute jumper descends in a vertical plane and contacts the ground upright. This, as a rule, is not the case. Such a landing could occur only if there were no wind currents.

Oscillation of the parachute is the biggest individual factor in the production of injuries, including fractures, among the jumpers. It is this oscillation that causes the jumper to contact the ground sideways, forward or backward.

The force of the impact with the ground can be compared to that of a man running and then jumping from a platform 12 feet (3.5 meters) high. There is that forward motion that is not appreciated by many persons. The men are

instructed to land on the balls of their feet and then go into a forward roll to absorb much of this particular shock. Metatarsal fractures constitute only about 5 per cent of the total number of fractures. As the actual percentages of the various types of fractures have been described previously by me,<sup>1</sup> no attempt will be made to elaborate on them here.

It may be mentioned that in frequency the most common individual fracture is that of the external malleolus—due to the same mechanism as that of the com-



Fig. 1.—Typical fracture of the posterior lip of the tibia. This usually occurs alone, and there is no appreciable separation of the fragments.

mon sprain of the ankle, i. e., adduction and inversion of the foot. Fractures of this type constitute 23 per cent of all the fractures seen among jumpers, with the ankle in a neutral position.

1. Tobin, W. J.; Cohen, L. J., and Vandover, J. T.: Parachute Injuries, *J. A. M. A.* **117**: 1318-1321 (Oct. 18) 1941. Tobin, W. J.; Ciccone, R.; Vandover, J. T., and Wohl, C. W.: Parachute Injuries, *Army M. Bull.*, April 1943.

From the anatomic point of view, the superior surface of the astragalus and the inferior articular surface of the tibia are parallel and perpendicular to the long axis of the tibia. With the foot in plantar flexion, the posterosuperior articular surface of the astragalus, which presents this structure's most narrow transverse diameter, is in contact with the articular surface of the tibia. In this position it is less firmly locked than in dorsiflexion. Normal plantar flexion is 145 degrees, but this is a variable figure. The posterior articular ligament is relaxed in plantar flexion—hence little or no support is presented to the force



Fig. 2.—Fracture of the posterior lip of the tibia associated with a fracture of the internal malleolus and an oblique fracture of the lower part of the shaft of the fibula.

transmitted upward through the long axis of the foot through the astragalus to the lower end of the tibia. The result is a "shearing" off of the posterior articular surface of the tibia, the so-called posterior lip or third malleolus.

As a routine procedure—whether the fracture of the posterior lip occurred alone or in junction with a fracture of the external malleolus—treatment consisted in immobilizing the joint for an average of four weeks in a skin-tight plaster cast with a walking iron attached. The incomplete fractures required less time than those in which separation of the fragments had taken place.

In cases of trimalleolar fracture, weight bearing was not instituted early, in fear of a separation of the malleoli. Fracture of this type has been considered sufficiently severe to justify recommending the jumper for a permanent nonjump status.

Jumpers with uncomplicated fracture of the posterior lip were allowed to return to jump training after an adequate period—seldom under three months.

In conclusion, it is felt that fracture of the posterior lip of the tibia is occurring frequently enough among the paratroopers to justify the introduction of the phrase "paratrooper fracture," as it is believed that in no other occupation does this particular fracture occur as frequently.

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## TORSION OF THE ACHILLES TENDON: ITS SURGICAL SIGNIFICANCE

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Lengthening the heel cord is the commonest single operative procedure in the repertoire of most orthopedic surgeons, and the reporting of any simplification of the technic seems justified, particularly if it brings to light an interesting embryologic phenomenon which explains the internal arrangement of the fibers of that structure, not generally appreciated. Before I developed my special but simple technic of subcutaneous tenotomy, I had abandoned that procedure because of frequent inability to get the severed tendon elements to slide apart, regardless of the near completeness of the alternate transverse cuts, and had employed an open tenoplastic technic, converting what should be a relatively simple operation into a much more formidable one.

The satisfaction that has long accompanied this lengthening procedure, together with the continual urging of my friends that I publish a description of the procedure, has finally prompted me to finish a task started many years ago, when it was submitted as a successful thesis. The paper was even read at one of the national meetings but, partly for the reason that the embryologic phase had not been thoroughly worked out and for various other reasons, it never appeared in print. A particularly favorable opportunity for publication has presented itself and I am most happy to have included in this volume a contribution which I feel has considerable value and which I believe has been my most important original contribution. I present it as a token of sincere appreciation for the opportunity in orthopedic surgery made possible for me by the one to whom this volume is dedicated.

The lengthening of the achilles tendon was really the first modern orthopedic operation to be performed and has continued to be the most frequent single procedure employed in this branch of surgery. It is relatively simple, but any one who has done it many times has been impressed by the difficulty frequently encountered before the partially severed tendon sections slide apart, and by how much of the tendon has to be severed before the lengthening is accomplished. Not infrequently the operator fears that he has completely severed the tendon at the proximal or the distal transverse cut and is far from being satisfied with a job that, with knowledge of the internal structure of the tendon, is so certain. Even when the tendon is generously exposed it is difficult to do a neat job without this information. The technic necessitating three transverse cuts is far from satisfactory, and although the desired results are finally accomplished, there is no comparison between the two procedures after one has done the lengthening operation a few times in the manner about to be described.

Any suggestion that can facilitate the performance of such an important and frequent operation I feel will be welcome, and the only apology that I believe to be in order at this time is that relative to the delay in publishing the technic after employing it for so many years myself.

In brief, the explanation of the difficulty encountered in lengthening the heel cord by simple subcutaneous tenotomies lies in the fact that there is approximately a 90 degree twist of the structure on its own axis within the surgical field and

that when even two thirds of the medial fibers have been severed at one level and two thirds of the lateral fibers at another level, enough fibers miss being cut to cause the tendon to "hang." An ordinary twisted Manila rope would behave in the same way if cut partially at different levels and cognizance were not taken of the twist to make appropriate cuts.

When this abnormality in the internal structure of the achilles tendon is appreciated (at least in comparison of this with other tendons) and the transverse partial tenotomies are made with it in mind, no difficulty is experienced in lengthening a tendon previously not operated on. If the anterior two thirds of the heel cord is severed a convenient distance above its insertion into the calcaneal tuberosity.



Fig. 1.—Photograph of the achilles tendons showing the torsion.

and the medial two thirds is severed 2 or 3 inches (5 or 7.5 cm.) above this point in an adult, no difficulty will be encountered in elongating the tendon by applying moderate dorsiflexion force to the forefoot in an uncomplicated equinus deformity. The exact technic employed calls for starting the proximal transverse tenotomy on the medial side of the tendon, after the anterior two thirds has been cut about 2 inches distally, continuing with it laterally until the tendon sections are felt to slide apart while the previously mentioned moderate dorsiflexion force is being applied to the forefoot. ♥

It is suggested that before this procedure is done subcutaneously it be done several times with the tendon exposed, until the mechanics of the situation is thoroughly appreciated and confidence established. Later it might be interesting as an occasional demonstration to do the subcutaneous procedure and then expose



the lengthened tendon to prove the efficacy of the operation. Ordinarily, of course, nothing is done but the properly located transverse tenotomies. 1

This torsion of the achilles tendon is not described in any modern anatomic textbook, although the artists in drawing many of the illustrations have frequently depicted this phenomenon accurately. The only discussion of this condition I have been able to discover appeared almost half a century ago—that of Parsons, who described the heel cord in the Canadian beaver. He does not say definitely but implies that the twist that he had noted in this industrious animal must be present in man.

I have dissected the commoner domestic mammals and found this same torsion to be present in each, and I assume that it must be present in all animals in which there occurs the peculiar rotation of the posterior tarsus on which this morphologic character depends.

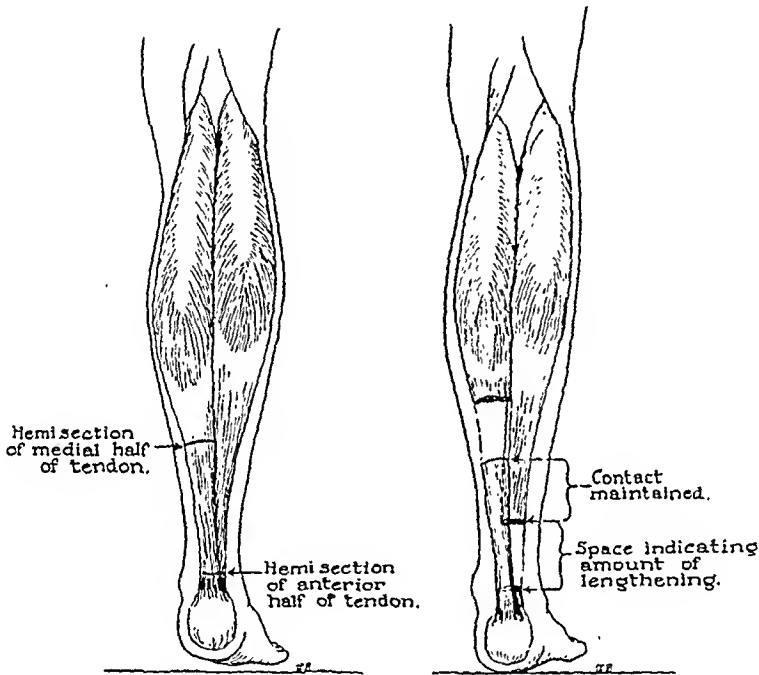


Fig. 2.—Drawings to illustrate the placing of the two specially directed partial transverse cuts, both of the right foot (courtesy of Dr. Clarence H. Heyman).

To understand the remarkable torsion phenomenon already referred to, one must briefly summarize the embryologic development of this apparently uncomplicated region. No one has yet been able to demonstrate accurately the very early stages by which the undifferentiated flipper-like limb bud develops into the structural formation of the ankle. The transition apparently occurs so quickly that sections of the limb buds showing this transition stage have not yet been obtained, and so the following explanation must be based largely on theory but, none the less, theory depending on anatomically recognized facts.

To explain successfully what one finds in the internal structure of the heel cord, one must assume that the anlagen of the os calcis and the astragalus are the os tibiale and the os fibulare, respectively, located at the ends originally of their corresponding bones. As the side by side relationship of these two anlagen changes to an under-over position, the tendinous portions of the muscular anlagen of the inner and outer heads of the gastrocnemius muscle inserted into the anlagen at the

distal ends of the tibia and the fibula rotate necessarily through an angle of 90 degrees while the corresponding 90 degrees' angulation of the ankle is being developed. Incidentally, it might be interesting to recall here that one derivation of the word "angle" is from this joint, which of course existed ages before man had any sort of language. The tendon of the outer head of the gastrocnemius muscle being inserted into the anlage of the os fibulare is carried at its insertion forward and above the insertion of the outer head into the tuberosity of the os calcis. The soleus muscle tendon continues between these two tendons until they all fuse into the tuberosity, losing its identity in man with the short flexor muscle of the toes, which apparently persists in all lower mammals, certainly the domestic animals which I have dissected personally.

As the tendons change their relationship from the side by side position to an anterior-posterior position, the tendon of the outer head becomes fused with the tendon of the inner head and loses its attachment to the os fibulare, now the astragalus, the soleus muscle tendon, as stated, evidently fusing between them, a fact which becomes apparent in a macerated specimen.

When the anterior portion of the heel cord is cut near its insertion into the os calcis, the fibers that remain uncut are the fibers from the inner head and are located on the medial portion of the large conjoined tendon proximally. Therefore when the medial portion of the structure is severed proximally, all fibers are severed and the sections slide apart with a minimum of effort.

While I am unable to follow the same analogy through, I feel sure that the crossing of the tendons of the peroneus longus muscle and the posterior tibial muscle in the forefoot is associated with this posterior tarsal rotation of the os calcis and the astragalus. To substantiate this further, one may recall the anatomic position of the upper extremity when the forearm is in full supination: i. e., the first digit is lateral, while in the foot the first digit is medial. The whole explanation is out of the field of the orthopedic surgeon and, it is anticipated, will some day be worked out accurately by the embryologist. It is hoped that the reader has not been too confused by this rather complicated discussion, which was deemed to be of sufficient interest to be included in this primarily clinical paper.

Regardless of the correctness of the explanation, the subcutaneous tenotomy using only the two specially directed partial transverse cuts permits the two tendon sections to be slid apart with sufficient ease to simplify the lengthening of the achilles tendon and is heartily recommended for routine use in this frequent orthopedic procedure.

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## REHABILITATION IN WARTIME BRITAIN

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During a recent tour of duty as surgeon in chief of the American Hospital in Britain (February to August 1942) I became interested in the problem of rehabilitation as faced by the Armed Forces of Great Britain. In the Churchill Hospital at Oxford my associates and I were de facto a reconstruction unit placed at the disposal of all branches of the services. A great many of the military patients were there as a result of accidents in the course of training and of accidents in transport. Others came from far off Libya, while there were even a few left over from Dunkirk. Thus there was a mixture of recent to moderately recent injuries, including both simple and compound fractures, together with older problems of nonunion and malunion, often associated with osteomyelitis, and always in these older problems there was the element of impaired function with its threat of permanent disability of a high degree. The sources of the most severe injuries were blasts and motorcycle accidents. In the former a man was often hurled through the air to receive multiple fractures and other injuries on encountering solid resistance. The same type of injury resulted when motorcycles driven at a high rate of speed skidded or otherwise went out of control on the wet winding narrow roads of England. These men sustained severe shock in addition to multiple fractures, and there were not infrequently internal injuries. In consequence, the primary problem of treatment was often that of preserving life, and the final treatment of the fractures aside from temporary splinting had to be postponed. By the time such patients were admitted to Churchill Hospital, four to six weeks had frequently elapsed. All in all, this group offered a serious challenge to our reconstruction group. Exactly similar problems were encountered in the various British military hospitals. Similar problems were sometimes found in civilians who were injured by air raids.

One of the primary lessons which has to be assimilated by one who turns from civilian to military surgical problems is that the primary purpose of an army is to fight battles and win the war. In England the purpose of the Royal Army Medical Corps is to restore men to front line duty, and if there is any man for whom that cannot be done, to discharge such a man from the Army and thus disencumber themselves of useless "debris." This greatly simplifies the problems of the Army and Navy medical services.

In practice the maximum period of disability within the Army has been arbitrarily set at one year. Inspection boards are created in each hospital region, and each man is examined by one or two medical officers at about three and seven months after injury and the findings reported to the central board together with the recommendations of the examiners. If at the three month period it is apparent that the injured man will not be able to regain usefulness to the Army within the year, he is at once discharged. Most of the patients are retained until the seven month examination, when there is a further determination of fitness, while a few may not have final judgment passed until the twelve month period is about completed. No man may be retained in the Army if he is unable to return to duty at the year's end. The Royal Navy, on the other hand, does not have any arbitrary

period for discharge but tends to keep the men on its list as long as active treatment is indicated or until the maximum of restoration has been accomplished.

Discharge from the Army for reason of continued disability did not mean that the man would be neglected. Responsibility merely passed from the Army to the Ministry of Pensions, which was then charged with the man's further treatment and with his ultimate education toward usefulness in civilian life on the basis of impairment. At Churchill Hospital this change of control usually permitted the patient to remain under treatment, with the sole change one of ultimate responsibility. Naturally, persons who had had amputations tended to become early charges of the Ministry of Pensions and were all concentrated at Roehampton under Mr. Perkins. Civilians who sustained disability became charges of the Ministry of Labor, whose duty it was to restore them to industry by training at various regional schools.

Primary rehabilitation, of course, was begun in the hospital. We were furnished by the British Ministry of Health with completely equipped departments of physical and occupational therapy. The personnel was British, and the members were efficient and exceptionally well trained. There were four physical therapists and a well equipped gymnasium (which was designed to be part of a receiving unit in case of emergency). The equipment consisted of various heat-producing units, including short wave machines, paraffin baths, wrist and forearm exercisers and other equipment standard in the better American hospitals. Occupational therapy was divided into carpentry work, which was directed by a practical joiner secured from Oxford, and knitting and weaving. The British soldier has a passion for embroidering his regimental coat of arms on anything from a pillow to a blanket. This is begun before he is able to sit up. Others knit and weave rugs. One of the great events of Churchill Hospital was the composition of a quilt bearing the insignia of every military unit represented at the hospital. The quilt was sent to President Roosevelt in honor of the American origin of this hospital. All of these activities and many others, begun early, diverted the patient's mind from his own problems and kept him busy. When weight bearing was begun, the patients began to wait on themselves and to walk outdoors where they worked in vegetable gardens, of which there was one for each ward. At this stage of convalescence they went to a central dining room for their meals.

At this point, more purposeful work was begun by "P. T. sergeants" (instructors in physical training), who put these men who were in the early stages of convalescence through limited drills designed to build up endurance and to combat habitual limping. Such patients were sent shortly to convalescent homes, which were manor houses taken over by the Knights of St. John of the British Red Cross. There, physical therapy and drills were continued while, at the same time, there was increased opportunity for outdoor activities, such as golf on improvised courses and bowling on the green. It should be noted that many of these patients were activated in casts with thick rubber blocks fastened to the soles. The problem of the habitual limp had concerned me in civilian practice only in connection with certain patients whom I had considered neurotic. In mass rehabilitation it has been discovered that it is a factor of major importance which must be met by early emphasis on the correct method of normal walking. The "P. T. sergeants" are equipped to cajole, entice or warn men to use both the heel and the toe.

As soon as healing is completed, the soldier is discharged to a rehabilitation camp, where his activity is rapidly increased until he is restored to full time duty.

All of our patients were sent to Westbury. Unfortunately, the soldiers were allowed only four weeks of such training, and we therefore tended to keep them under care in one of the convalescent homes until we were certain that four weeks of fairly strenuous activity would enable them to return to active duty. The result was prolongation of hospitalization with delay in final recovery. By far the better system was that of the Air Force, largely organized by Watson Jones. We were privileged to visit their center for the rehabilitation of noncommissioned officers at Hoylake near Liverpool. Patients are sent there as soon as it is felt that benefit will result from rehabilitation treatment. If their condition is such that they will be unable to resume flying, they are prepared, if possible, for ground duty. All who are sent there are judged able eventually to resume duty in one of these categories.

The Air Force occupied a peculiarly privileged place in England at the time of our visit. Of all the troops in England, they alone were in constant fighting contact with the enemy. Constant and successful efforts were made before and after the beginning of the war to build up a splendid morale peculiar to the service. Since their heroic work in the battle of Britain, nothing has been too good for them. They eat the best food obtainable in Britain and are granted more frequent short leaves than ground troops. They wear a distinctive uniform, and it is worn with a sense of pride. When they are injured, the problem of rehabilitation is both physical and psychologic. The most frequent injuries are burns and fractures, while the mental stress at the time of injury is frequently severe. Some of these boys had drifted in the water for from hours to days with severe injuries before being rescued. Others had received compound fractures from wounds received over France or Germany. In addition there were the usual training injuries of a large air force concentrated in a small island. In Oxford County alone there was one crash every twenty-four hours.

At Hoylake all the men were given the unusual privilege of sleeping until 7:30 in the morning. The program began at 10 a. m. and continued until 5 p. m., with an hour out for luncheon. Each man was assigned to a group, and the activities of the group changed every hour. These activities, for the most part, consisted of games which were fun to play and would cause the man to forget himself for the moment. Each group, of course, was graded according to the stage of recovery. Thus treatment of a man was begun as soon as he was able to wear a walking cast and consisted of squad drill, volley ball, sawing wood and physical therapy. Walking was made possible by fastening a rubber or felt square to the under heel of the cast. No walking irons were permitted, and I found that all medical officers were firmly of the opinion that walking irons contribute to the formation of a habitual limp, difficult to eradicate and persisting for a long time. Drill was in charge of physical training sergeants, who taught the men at the start to do heel and toe walking. Two separate hours a day were given to this activity.

Those who were capable of advanced training played tennis and volley ball, ran races and played a wonderful and strange combination of basket ball and rugby football which had been invented for boy scouts by the King. The field was about half the size of a football field. The ball could be advanced by passing, kicking or running. Goals were made by putting the ball in the basket. For purposes of safety, body tackling was eliminated in favor of touch tackling.

In addition to taking part in these and other games, each man spent a half hour with a physical therapist, during which baking and diathermy were given in addition to active local stretching exercises. But, of all that we saw, the most

unexpected sight was a dance hall wherein an array of limping men were gaily dancing to the tunes of records with very nice girls who came on schedule from Liverpool to carry out a fairly pleasant assignment. The morale officers made much of this activity and informed us that it was an important bridge for the advanced patients back into normal activity. One almost detected one's self limping hopefully. All in all, I was impressed by the fact that all of these activities were obviously fun to those participating. It did lead to a degree of activity which was almost unbelievable in a fairly short time. Constantly in the background were morale officers who were watchful for any evidence of psychologic breakdown. We were told that there was a very low but constant percentage of men who, for the latter reason, were eventually lost to the Air Force: the men who had lost their nerve.

The camp was an inspiring object to any orthopedic surgeon and should serve as an example to the Army of the United States. Up to August 1, the time of our departure, there had been no evidence of such interest. It was a time of hurried organization by the Surgeon General in England, who had first to secure and establish hospitals, organization and supplies, and this problem may have come up for study since. One could not help but reflect on the use to which a modified organization of this type could be put in peace times. Certainly rehabilitation centers organized along these lines would be a great boon to injured industrial workers, with places for the teaching of new skills to those unable to return to their former occupations. Until industrial commissions, employers and labor itself acquire a social point of view, such prospects are well nigh hopeless. Some day it will surely become recognized that the cheapest method of paying the cost of injuries will be along these lines. As long as penny pinching is the chief aim, the money of compensation will continue largely to occupy the minds of many injured employees.

Our experience in England revealed much the same class of problems that try us here in civilian practice. For instance, the problem of the femoral fracture is now fairly well solved by the means at hand if the surgeon has been adequately trained. The problem of the resulting stiffened knee is far from solved. Brigadier Bristow made the statement that not a single man treated for femoral fracture with displacement had been rehabilitated for service in the British Army one year after injury, the time for discharge of disabled soldiers. On the other hand, we saw many with 90 degrees of motion at the Air Force camp at Hoylake as testimony to the excellent results obtained by the methods just described. We had some similar results in patients treated by the Roger Anderson method. This apparatus permits only about 30 degrees' flexion during its use because the lower pins impinge on the vastus externus muscle, but this 30 degrees gives a good amount of activity and the amount quickly moves up once the pins are removed. It permits the patient to be up and about, with great advantage to his general condition. There is a great misunderstanding as to the time of healing of these fractures. The average is twelve to fifteen weeks, not eight. In eighteen years I have seen only one adult whose fracture healed solidly in eight weeks. Immobilization for this prolonged time of course makes the knee the problem that it is. Careful use of skeletal traction with motion by means of a Pierson attachment is an equally valid method of combating stiffness. There is evidence, however, suggesting that skeletal traction may be the cause of an increase in the percentage of delayed unions, while traction through the knee joint is thought by many to be an influence favoring stiffness.

Too many patients on weight bearing are left to the device of walking to bring about increase of knee motion. Analysis of the gait shows that knee flexion is

purely a passive accident, incident to momentary lagging of the foot on the ground as the body weight is carried forward on the opposite leg. To flex the knee actively, the hamstrings must be used with the femur fixed to prevent hip flexion. This can be accomplished only by lying on the face and raising the foot off the table by active use of the hamstrings. The other method is that of walking backward.

Then, there is the problem of the unstable knee, due either to tear of lateral ligaments or to generalized muscular weakness of the leg. Both accomplish the same result by somewhat different mechanisms. Watson Jones demonstrated a number of such knees before and after rehabilitation treatment and stated that he had for some time given up surgical repair of the ligaments of the knee in favor of muscle training because he had found that under such treatment the knees all became functionally stable.

In conclusion I would say that a brief six months' experience with war injuries in England has greatly sharpened an interest in rehabilitation which was already fairly keen. As one grows older in orthopedic surgery the lag of function after skeletal repair makes a more and more serious impression. It would seem that our methods of securing purely physical repair have become so varied and adequate that our greatest concern should now lie in securing quicker and better return of function, for it is by function that men live.

# ARCHIVES OF SURGERY

## EXPERIMENTAL GASTRIC CARCINOMA

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National Cancer Institute

### INTRODUCTION

This review reconsiders the facts on which experimental gastric cancer has been produced. Briefly it points out the peculiarities of the human gastric mucosa and compares it with that of other species. The recognized precancerous conditions of the mucosa are then described, and special consideration is given to the concept of the possible origin of gastric cancer from a chronically damaged mucosa. The multiplicity of factors, secondary, environmental or hereditary, which might produce this alteration are considered. No claim is made for causal connection. Possible points for experimental attack are discussed.

Its inaccessibility has gained for gastric cancer a certain element of mystery which has tended to set it apart from other forms of neoplasia. Yet when the severely altered structural background out of which gastric cancer arises is understood it is apparent that its origin is not particularly different from that of other carcinomas, for instance cutaneous cancer arising in the dermis after chronic injury by roentgen rays. The stomach does not offer ideal conditions for the study of the formal genesis of carcinoma, the mechanism of its origin from the normal cells: so experimental work should be directed at determining the many environmental factors which are thought to be involved in its causal genesis. The inciting factors which lead to development of malignant neoplasms may at present be partially ferreted out, so as to be correlated with the actual occurrence of the carcinoma. Among such factors are gastric mucosal changes known to be associated with or to exist prior to malignant lesions, and environmental agents. By sorting out existing knowledge, sound deductions capable of experimental proof may be secured.

A comparison may be made of the results obtained from experimental surgery of the stomach and those obtained from the experimental attack on gastric cancer. The problem of cancer of the stomach and its many associated problems have been better solved because the solution stemmed from experimental surgery. The concept of human gastric surgery of the whole Billrothian era was based on resections which had been performed on animals. In comparison with the surgical approach to therapy, experimentation to determine fundamental causation and pathogenesis has been unsuccessful. The failures are here comparable to, if not greater than, those met with in direct study of the human disease. The results have been well nigh consistently negative and at times so confusing as to make them tenuous beyond value. The experimenter on animals has been restricted from the start because of the rarity of spontaneous adenocarcinoma of the stomach



in laboratory animals,<sup>1</sup> although an adenomatous lesion of common occurrence in one strain of mice has been described.<sup>2</sup> In early studies on production of gastric cancer in which a parasitic nematode was used<sup>3</sup> it was found later that the animals had been kept on an incomplete diet. This, of course, invalidated the theory that the parasite was necessarily the inciting agent.<sup>4</sup> The interpretation of the observed lesions was difficult. For instance a squamous metaplasia found in the lung was mistakenly described as metastatic carcinoma.<sup>5</sup> Soon after their discovery the carcinogens were used in feeding experiments. These experiments, after some mistrials, led to development of squamous cell carcinoma of the forestomach<sup>6</sup> (a nonglandular portion lined with squamous epithelium) in smaller laboratory rodents. This lesion is comparable to carcinoma of the esophagus in man. Cognizance of the pessimistic outlook for experimental work coupled with a continued high mortality from gastric cancer caused the National Advisory Cancer Council to call a conference on gastric cancer, which was held on Oct. 11 and 12, 1940.<sup>7</sup> This conference brought together experts in the many specialties which can now be utilized in solving the problem. Here was proposed the first extensive concerted effort toward both a clinical and an experimental attack on the problem, indeed a much needed key. A historical review on experimental gastric cancer was published in the same symposium.<sup>8</sup>

#### EXPERIMENTAL APPROACH

Since the major problem of gastric cancer for the time being is its causation, the experimental data must perforce be those most applicable to the manifestations of the human disease. The relative importance of the association of gastric cancer with chronic gastritis, ulcer and environmental factors must be determined. It is pertinent to ask what further gain may be expected from animal experimentation. The question has been answered by pointing out that investigators expect to acquire new physiologic knowledge and subsequent understanding of pathologic processes.<sup>9</sup> In addition, well defined conditions make it possible to understand and control the agents and to supply the unknown links, with the idea of instituting preventive measures. In order to test experimentally the obser-

1. Wells, H. G.; Slye, M., and Holmes, H. F.: *Comparative Pathology of Cancer of the Alimentary Canal, with Report of Cases in Mice: Studies in Incidence and Inheritability of Spontaneous Tumors in Mice*, *Am. J. Cancer* **33**:223-238, 1938. Feldman, W. H.: *Neoplasms of Domesticated Animals*, Philadelphia, W. B. Saunders Company, 1932, p. 68. Slye, M.; Holmes, H. F., and Wells, H. G.: *Comparative Pathology of the Stomach with Particular Reference to the Primary Spontaneous Malignant Tumors of the Alimentary Canal in Mice*, *J. Cancer Research* **2**:410-425, 1917.

2. Stewart, H. L., and Andervont, H. B.: *Pathologic Observations on Adenomatous Lesion of Stomach in Mice of Strain I*, *Arch. Path.* **26**:1009-1022 (Nov.) 1938.

3. Fibiger, J.: (a) *Weitere Untersuchungen über das Spiroptercarcinom der Ratte*, *Ztschr. f. Krebsforsch.* **14**:295-326, 1914; (b) **13**:217-280, 1913; (c) *J. Cancer Research* **4**:367-387, 1919.

4. Passey, F. D.; Lees, A., and Knox, J. C.: *Spiroptera Cancer and Diet Deficiency*, *J. Path. & Bact.* **40**:198-199, 1935.

5. Wolbach, S. B., and Howe, P. R.: *Tissue Changes Following Deprivation of Fat-Soluble A Vitamin*, *J. Exper. Med.* **42**:753-777, 1925.

6. Waterman, N.: (a) *Cancer expérimental de l'estomac; son rapport avec la g n se du cancer de l'estomac humain*, *Bull. Assoc. franc. p. l' tude du cancer* **29**:70-76, 1940; (b) *Production of Carcinoma of Stomach in Mice by 3,4 Benzpyrene*, *Acta brev. Neerland.* **7**:18-20, 1937.

7. *Conference on Gastric Cancer*, *J. Nat. Cancer Inst.* **1**:423-558, 1941.

8. Klein, A. J., and Palmer, W. L.: *Experimental Gastric Carcinoma: A Critical Review with Comments on the Criteria of Induced Malignancy*, *J. Nat. Cancer Inst.* **1**:559-584, 1941.

9. Voegtlin, C.: *Program for Study of Cancer of the Stomach*, *J. Nat. Cancer Inst.* **1**:539-558, 1941.

various made on human subjects the research worker must choose the correct animal and devise most carefully controlled conditions, so that each factor under observation may be weighed and either discarded or recognized as a precancerous condition. Each time factor and every physical element must be precisely considered. Just now the goal should be the production of those lesions most seriously thought to be precancerous or most often found associated with cancer.

To appreciate the time factor involved the investigator may compare cancer of the stomach originating from a long-damaged mucosa with cancer originating from the better known types of chronic precancerous lesions. Although the skin is not a mucous membrane, it affords an ideal place for this comparison. Paget's and Bowen's dermatoses show a prolonged chronic course prior to their manifest cancer phase. Reduced functions occur in these conditions, and so it is commonly with cancer of the stomach. Length of time is the impressive thing. Is time necessary in order to allow extrinsic factors to act? It is not proved, but it may be that aging is the essential element. If time rather than physiologic aging is of most importance, experiments which run a year or so would be of use. However, at least in man, it would appear that aging is of primary import. Probably the most common error has been that of performing experiments of relatively short duration. Clinical reports on gastric cancer stress repeatedly the length of time the preconditions must exist,<sup>10</sup> a train of events thought to run through a period of twenty years or more. It is suggestive, too, that the average age-specific mortality rate for gastric cancer is, as for other forms of gastrointestinal cancer, progressive with age.<sup>11</sup> Among white persons the mean age at time of death from this disease is 65 years<sup>11</sup> and the maximum number of deaths in any one ten year age period occurs between the ages of 65 and 74.<sup>12</sup> Previously the peak was in an earlier age period. If experiments are to be significant, they must be based on the statistically important series of etiologic events which occur during the aging of the gastric mucosa. These are believed to be largely extrinsic in nature.<sup>12</sup> To have an etiologic significance, the events must occur in the series frequently enough to be beyond the realm of chance. It is at this precise point that the histogenic basis is useful, to place the sequence of events in a reasonable time relationship and to make certain that there is a true association between two events. An instance of not using this type of reasoning is the attempt to produce gastric cancer on the basis of acute ulcer. All known carcinogens, even the most potent, are known to bring about primary damage of tissues in the intact body by a process involving time<sup>14</sup> and followed by a long induction period. An animal such as the monkey or dog, whose life span and whose anatomic functions to some extent approximate those of man, should be used, so that all elements may be allowed a sufficient time for action. In addition, its complex nature makes one recognize the multiplicity of factors which may contribute to the development of gastric cancer; it is not believed to arise from a single condition.

10. Hurst, A. F.: Cancer of the Alimentary Canal, *Lancet* 1:553-558, 1939.

11. Cancer Mortality in the United States: IV. Age Variation in Mortality from Cancer of Specific Sites, 1930-1932, Public Health Bulletin 275, United States Public Health Service, 1941.

12. Vital Statistics of the United States, 1939: I. Natality and Mortality Data for the United States Tabulated by Place of Occurrence with Supplemental Tables for Hawaii, Puerto Rico, and the Virgin Islands, United States Department of Commerce, Bureau of the Census, 1941, p. 153.

13. Herbert, W. E., and Bruske, J. S.: Etiology of Cancer of Stomach, *Guy's Hosp. Rep.* 86:301-308, 1936. Lintott, G. A. M.: Etiology of Cancer of Stomach: Factors Involved in Varying Incidence in Different Classes and Different Countries, *ibid.* 86:293-300, 1936.

14. Woglom, W. H.: Experimental Tar Cancer, *Arch. Path.* 2:533-576 (Oct.); 709-752 (Nov.) 1926.

COMPARISON OF HUMAN GASTRIC STRUCTURE AND FUNCTION WITH  
THOSE OF OTHER SPECIES; MILIEU OF GASTRIC MUCOSA;  
NORMAL REGROWTH FOLLOWING TRAUMA

The human gastric mucosa, with its four zones (cardiac, fundic, intermediate and pyloric) and its own particular distribution of peptic and oxyntic cells, cannot be exactly duplicated in any species, but, as might be expected, monkeys and apes do have a similar type of mucosa.<sup>15</sup> Probably the most practical animals to work with, and those on which the most extended studies have been done, are the dog, cat, pig, rabbit and guinea pig.<sup>16</sup> These species have a gland-lined gastric mucosa, and although the distribution of cells is characteristic for each species they are sufficiently similar to be of use. Of these animals, dogs of a long-lived strain would probably be ideal. The stomach of the small laboratory rodent is half lined with squamous epithelium, and, although it is known to be highly sensitive to carcinogens,<sup>17</sup> its dissimilarity to the human stomach makes it hardly perfect for reproducing conditions found in man.

Since by the direct injection of a powerful carcinogen adenocarcinoma of the stomach has been recently produced in mice,<sup>17</sup> it is probable that some factor (time, aging?) other than mere species resistance is responsible for its uncommon spontaneous occurrence. Perhaps adenocarcinoma would be more frequent if enough animals of species closely allied to man could be kept alive to a sufficiently old age. Unfortunately, the lives of most laboratory animals are terminated in youth or middle age. Since it is far from certain that the physiologic aging rate in a short-lived species is actually proportionate to its life span, such animals cannot be considered satisfactory for reproducing the conditions under which gastric carcinoma occurs in man.

The stomach is a gland-lined structure which is subject to powerful and rapidly changing influences. Besides the ever modified flow of gastric juice<sup>18</sup> there is dumped into it at irregular intervals an endless array of all sorts of damaging agents. More the marvel, then, that after injury the mucosa can heal at all! Even after extensive ulceration total healing may take place in a period of ten days. How healing of the acutely damaged and the more gradually destroyed mucous membrane comes about is poorly understood. Experimentally produced defects of the mucous membrane over a large area may be completely repaired in the dog with replacement of the glands in a normal-appearing mucosa.<sup>19</sup> The first part of the epithelium to regenerate contains glands made up only of mucous cells in the neck of the gland, and it is from these that the characteristic chief

15. Straus, W. L.: *The Thoracic and Abdominal Viscera of Primates with Special Reference to the Orang-Utan*, Proc. Am. Phil. Soc. 76:1-85, 1936. Maximow, A. A.: *Textbook of Histology*, Philadelphia, W. B. Saunders Company, 1931, p. 512. Wollard, H. H.: *The Anatomy of Tarsius Spectrum*, Proc. Zool. Soc. London, 1925, pp. 1071-1184.

16. (a) Sisson, S., and Grossman, J. D.: *The Anatomy of the Domestic Animals*, Philadelphia, W. B. Saunders Company, 1941. (b) Reighard, J. E., and Jennings, H. S.: *Dissection of the Cat*, New York, Henry Holt & Company, Inc., 1935. (c) Lim, R. K. S.: *The Gastric Mucosa*, Quart. J. Micr. Sc. 66:187-213, 1922. (d) Cowdry, E. V.: *Special Cytology*, New York, Paul B. Hoeber, Inc., 1932, vol. 1. (e) Nettleship, A.: *Guinea Pig and Cat*, unpublished data.

17. Stewart, H., and Lorenz, E.: *Induction of Adenocarcinoma of Pyloric Stomach in Mice by Methylcholanthrene (Preliminary Report)*, J. Nat. Cancer Inst. 2:193-196, 1941.

18. Carlson, A. J.: (a) *The Condition of the Digestive Tract in Parathyroid Tetany in Cats and Dogs*, Am. J. Physiol. 30:309-340, 1912-1913; (b) *The Secretion of Gastric Juice in Health and Disease*, Physiol. Rev. 3:1-40, 1923.

19. Ferguson, A. N.: *A Cytological Study of the Regeneration of the Gastric Glands Following Experimental Removal of Large Areas of the Mucosa*, Am. J. Anat. 42:403-441, 1928.

of the gland cells. These cells remain after the more specialized secretory cells have been destroyed. Once the mucous membrane is seriously damaged it may not recover, or, even when new tissue which seems morphologically normal appears, it may be unable to return to a functionally active state. While it is possible that different types of cells recover in different fashion, their ability to withstand the same amount of damage is not similar. Investigators are uninformative as to how extensive the lesions must be or what kind of damaging agent must be applied to the glands before they stop secreting. In the chronically damaged mucosa it has been concluded that various extrinsic factors are at play, since the majority of altered cells may be within the ducts or within the acini. The predominant type of gastric cancer arises from cells which line the ducts, although a small cell acinar cancer from the chief cells is also known.

#### ABNORMAL CONDITIONS OF MUCOSA ASSOCIATED WITH CARCINOMA: THEIR POSSIBLE CAUSAL RELATIONSHIP

At the present juncture it is short sighted to expect carcinoma of the stomach to arise *de novo*. It is now believed there are two conditions of the gastric mucosa from which the evolution of gastric cancer is constant, polyp<sup>21</sup> and carcinoma in situ.<sup>22</sup> Then there is a group of conditions which may result in malignant changes, or which are most commonly associated with gastric cancer.

As to polyp, Borrmann<sup>23</sup> and others have given adequate descriptions of what is now generally recognized as polyp with malignant transformation. One no longer questions the malignant potentialities of this lesion. Carcinoma in situ, or preinvasive carcinoma, has been described from well authenticated cases by Mallory,<sup>24</sup> and previously by others. The validity of their classification must not be doubted because of discovery of an in situ lesion in a new site. Carcinoma in situ may be accepted as the earliest discernible morphologic form, the development of similar malignant lesions having been worked out in other organs (Schiller<sup>25</sup> and Broders<sup>24</sup>). The prolonged time which may elapse before any form of carcinoma in situ becomes frankly invasive has been stressed by all authors who have written about it.

A number of clinicopathologic studies substantiate the belief that there are precancerous lesions of the gastric mucosa which may become malignant, such as chronic gastritis, with or without achlorhydria and with or without pernicious anemia, and chronic ulcer. Of the two conditions chronic atrophic gastritis is most commonly found associated with cancer as described in classic papers by Konjetzny.<sup>25</sup> He has been well backed by Orator,<sup>26</sup> Stewart<sup>27</sup> and others.<sup>28</sup>

20. Popoff, N. W.: Pathology of the Stomach, Arch. Path. 31:220-267 (Feb.) 1941.

21. Borrmann, R.: Geschwülste des Magens und Duodenum, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, pt. 1, pp. 812-1054.

22. Mallory, T. B.: Carcinoma in Situ of the Stomach and Its Bearing on the Histogenesis of Malignant Ulcers, Arch. Path. 30:348-362 (July) 1940.

23. Schiller, W.: Early Diagnosis of Carcinoma of Cervix, Surg., Gynec. & Obst. 56:210-222, 1933.

24. Broders, A. C.: Carcinoma in Situ Contrasted with Benign Penetrating Epithelium, J. A. M. A. 99:1670-1674 (Nov. 12) 1932.

25. Konjetzny, G. E.: (a) Der Magenkrebs, Stuttgart, F. Enke, 1938; (b) Der oberflächliche Schleimhautkrebs des Magens, Chirurg 12:192-202, 1940; (c) Bemerkungen zu dem Aufsatz von Haring, "Welche Bedeutung besitzt die chronische Gastritis für die Entstehung des Magenkrebses?" Med. Klin. 35:1456-1458, 1939.

26. Orator, V.: Beiträge zur Magenpathologie: II. Zur Pathologie und Genese des Carcinoms und Ulcuscarcinoms des Magens, Virchows Arch. f. path. Anat. 256:202-229, 1925.

Although chronic gastritis is a broad entity, its chief manifestations are heavy infiltration of chronic inflammatory cells into the mucosa and submucosa, atrophy and loss of glands and/or hyperplasia of glandular epithelium with cyst formation, and an increase in fibrous connective tissue in the two inner coats. All of these elements may vary except the atrophy and loss of glands. This is constant. Along with this and of more or less regular occurrence is achlorhydria. Although there are claims that there are no cases of carcinoma of the stomach in which free hydrochloric acid is present in the early stages of the disease and disappears in the later stages, this view is contradicted. Walters<sup>29</sup> found that approximately one third of his patients with carcinomatous lesions of the stomach had symptoms characteristic of ulcer. It may be said that achlorhydria is the rule, except with growths which arise on the basis of chronic ulcer. Perhaps the hypoacidity of age is important. Popoff<sup>30</sup> pointed out that it is uncommon to find normal production of acid in a person over the age of 35 and that 40 per cent of all persons over 50 have a diminution of acid. He expressed the opinion that the progressive senile atrophy of the functional mucosa which develops with advancing age may be related definitely to gastric hypofunction and anacidity. All deviations due to aging tend toward a decrease in pepsin and hydrochloric acid. Is this a pre-conditioning factor? The usual topographic placement of adenocarcinoma in the stomach suggests secondary factors yet unknown. Although there have been extended studies directed at the production of pernicious anemia by means of various gastric resections,<sup>30</sup> there have been few attempts at induction of atrophic gastritis in animals. A spontaneous lesion strikingly similar to that in man has been observed in monkeys.<sup>31</sup> Chronic atrophic gastritis may not be too rare a lesion in older animals of other species.

The microscopic studies on chronic gastritis associated with carcinoma<sup>32</sup> have not been done with the idea of comparing the lesion with the atrophic gastritis of pernicious anemia.<sup>33</sup> The lesions appear to be similar; however, Magnus pointed out differences.<sup>34</sup> It is held that the atrophic gastritis which accompanies pernicious anemia must destroy a large number of argentaffine cells before pernicious anemia is manifest.<sup>35</sup> It is not surprising that carcinoma may occur with pernicious anemia. Because more extensive studies have been made on this type of gastritis, it has been possible to learn a great deal about the ability of the gastric mucosa to regen-

27. Stewart, M. J.: Observations on the Relation of Malignant Disease to Benign Tumors of the Intestinal Tract, *Brit. M. J.* **2**:567-569, 1929.

28. Hurst, A. F.: Precursors of Carcinoma of the Stomach, *Lancet* **2**:1023-1028, 1929.  
Faber, K. H.: Gastritis and Its Consequences, New York, Oxford University Press, 1935.  
Schindler, R., and Smith, W. H.: Anacidity and Gastritis Associated with Gastric Carcinoma, *Am. J. Digest. Dis.* **9**:340-342, 1942.

29. Walters, W.: Malignant Lesions of the Stomach, *J. A. M. A.* **117**:1675-1679 (Nov. 15) 1941.

30. Jones, C. M.; Benedict, E. B., and Hampton, A. O.: Variations in Gastric Mucosa in Pernicious Anemia: Gastroscopic, Surgical and Roentgenologic Observations, *Am. J. M. Sc.* **190**:596-610, 1935.

31. Fairbrother, R. W., and Hurst, E. W.: Spontaneous Disease Observed in Six Hundred Monkeys, *J. Path. & Bact.* **35**:867-873, 1932.

32. Magnus, H. A., and Ungley, C. C.: Gastric Lesion in Pernicious Anemia, *Lancet* **1**:420-421, 1938. Konjetzny.<sup>25</sup>

33. Haring, W.: Gutartige Magengeschwülste bei perniziöser Anämie, *München. med. Wchnschr.* **85**:1544, 1938. Brown, M. R.: The Pathology of the Gastrointestinal Tract in Pernicious Anemia and Subacute Combined Degeneration of the Spinal Cord, *New England J. Med.* **210**:473-477, 1934.

34. Magnus, H. A.: Investigation of the Pathology of Gastritis with Reference to a Precancerous Condition of the Mucosa, *St. Barth. Hosp. Rep.* **70**:314-317, 1937.

35. Jacobsen, W.: The Argentaffine Cells and Pernicious Anemia, *J. Path. & Bact.* **49**:1-19, 1939.

data. The reports are at variance. The most recent data tend to show regeneration in patients given liver therapy<sup>36</sup>; the regeneration may or may not be complete, but it does cause regression of both the atrophy and the hyperplasia. Thus even an externally damaged mucosa still carries in it the potentialities of rapid regrowth, a condition one would assume to be necessary for the origin of neoplasia.

The argument that chronic ulcer gives rise to cancer of the stomach is an old one. The greatest incidence has been assumed to occur in prepyloric ulcers, although recent data tend to disprove the idea and to place the true incidence of malignant gastric ulcers between 10 and 12 per cent.<sup>37</sup> The clinicians with the broadest experience usually conclude that a certain percentage of their patients with cancer of the stomach have a precedent history of chronic ulcer. There are laboratory findings of hyperacidity to back this. Magnus<sup>38</sup> and others have pointed out that local gastritis particularly is a fairly constant occurrence in cases of chronic ulcer. Here the mucosa is doubly damaged. Since this argument has raged so long, it is surprising that there is so little experimental proof. There are now a number of ways to produce chronic gastric ulcer.<sup>39</sup> It would be a relatively simple matter to produce chronic ulcer and allow the necessary time for malignant change. This experiment should be done.

The early literature reports that much time was devoted to studying the heterotopic intestinal mucosal glands which occur commonly in the gastric wall. Now it is believed that most of such abnormal structures are brought about by a metaplasia of the gastric glands resulting from faulty regeneration and that relatively few carcinomas arise from true heterotopia.<sup>34</sup>

Crucial experiments are needed to establish the positive relationship between the conditions most commonly associated with gastric cancer and the cancer itself. It may be possible to reproduce these conditions by arranging experimentally the environmental factors thought to produce them. Those supposed environmental agents have served as a framework for the majority of experiments on gastric cancer which have heretofore been done.

#### ENVIRONMENTAL AND INTRINSIC FACTORS WHICH AFFECT THE MUCOSA

The great majority of investigations on experimental gastric cancer are based on the use of agents thought to produce the disease. The clinical studies are to be elucidated by experimental studies.

36. Schindler, R., and Serby, A. M.: Gastroscopic Observations in Pernicious Anemia, *Arch. Int. Med.* **63**:334-355 (Feb.) 1939. Faber, K., and Bloch, C.: Ueber die pathologischen Veränderungen an Digestionstractus bei der perniziösen Anämie, und über die sogenannte Darmatrophie, *Ztschr. f. klin. Med.* **40**:98, 1900. Wallgren, I.: Ueber die Veränderungen des Verdauungskanal bei der perniziösen Anämie, *Arb. a. d. path. Inst. d. Univ. Helsingfors* **3**:275-370, 1925.

37. Kirklin, B. P., and MacCarty, W. C.: Incidence of Malignancy in Prepyloric Ulcers, *J. A. M. A.* **120**:733-735 (Nov. 7), 1942.

38. (a) Wolfer, J. A.: Chronic Ulcerations in the Dog's Stomach Produced by X-Ray, *Proc. Soc. Exper. Biol. & Med.* **23**:45-47, 1925. (b) Churchill, T. P., and van Wagoner, F. H.: Cinchophen Poisoning, *ibid.* **28**:581-582, 1931. (c) Ivy, A. C., and Shapiro, P. F.: Studies on Gastric Ulcer: III. The Experimental Production of Gastric Ulcer by Local Allergy; Preliminary Report, *J. A. M. A.* **85**:1131 (Oct. 10) 1935. (d) Dodds, E. C.; Noble, R. L., and Smith, E. R.: A Gastric Lesion Produced by an Extract of the Pituitary Gland, *Lancet* **2**:918-919, 1934. (e) Dodds, E. C.; Cutting, W. C.; Noble, R. L., and Williams, P. C.: Pituitary Control of Alimentary Blood Flow and Secretion, *Proc. Roy Soc., London, s.B* **123**:27-59, 1937.

*Heredity.*—Does the hereditary factor work through the failure of gastric secretion? The tendency to achylia gastrica which accompanies age may certainly be more strongly pronounced in certain families than in others. In cases in which the added gravity of pernicious anemia has caused the patient to seek medical attention such familial traits have been discovered.<sup>39</sup> The most common finding has been the occurrence of 2 or more cases in the same family. None of these studies has ruled out what might be termed the "family eating complex." Every family has unwritten but no less established rules which govern its eating habits. These may be an uncontrollable factor in studies of hereditary traits. It is not clear whether the hereditary transmission of gastric polyp is similar to that of polyp of the large intestine. If so, it may be said to be inherited.<sup>40</sup> Experimentally it has not been practical to attack this aspect, simply because no strain of animal studied has a sufficient incidence of either polyposis or carcinoma. An adenomatous lesion in the I strain of mice has been reported.<sup>2</sup>

*Endocrine Glands.*—Changes due to abnormality of the endocrine glands would be expected to be functional in character. Hyperthyroidism causes either hypochlorhydria or achlorhydria.<sup>20</sup> Injections of solution of posterior pituitary produce ulceration of the gastric mucosa.<sup>38d</sup> This lesion in rabbits is intense engorgement and hemorrhage of the mucosa followed by acute necrosis of the entire acid-bearing area of the mucosa, with complete regeneration in about ten days. In a certain percentage of cases a chronic punched-out ulcer appears. This effect may be important in the genesis of ulcer. Schiffrin<sup>41</sup> has shown by experiments on dogs that an injection of parathyroid extract produces a decrease in the volume and acidity of the gastric contents.

*Neurofunctional Factors.*—The classic case of Cushing launched many experiments on the effect of the midbrain on the stomach. The most extensive lesions obtained by destruction of the tuber nuclei are superficial erosions.<sup>42</sup>

*Secretory Studies.*—From the experimental standpoint what is there to explain the functional achlorhydria of gastric cancer? Achlorhydria can occur without morphologic evidence.<sup>20</sup> Brunschwig<sup>43</sup> was able to demonstrate a secretory depressant in the gastric juice of patients with pernicious anemia and carried the work further to show a potent depressant in the extracts of achlorhydric carcinomatous stomachs.<sup>44</sup> The need for a quantitative method to study this substance is suggested. Ivy's quantitative enterogastrone method<sup>45</sup> might be applied. Entero-

39. Wilkinson, J. F., and Brockbank, W.: Importance of Familial Achlorhydria in Etiology of Pernicious Anemia, *Quart. J. Med.* **24**:219-238, 1931.

40. Dukes, C.: Hereditary Factor in Polyposis Intestini, or Multiple Adenomata, *Cancer Rev.* **5**:241-256, 1930.

41. Schiffrin, M. J.: Relationship Between the Parathyroid and Gastric Glands in the Dog, *Am. J. Physiol.* **135**:660-669, 1942.

42. Watts, J. W., and Fulton, J. F.: The Effect of Lesions of the Hypothalamus upon the Gastrointestinal Tract and Heart in Monkeys, *Ann. Surg.* **101**:363-372, 1935. Hoff, E. C., and Sheehan, O.: Experimental Gastric Erosions Following Hypothalamic Lesions in Monkeys, *Am. J. Path.* **11**:789-802, 1935. Keller, A. D.: Ulceration in the Digestive Tract of the Dog Following Intracranial Procedures: Preliminary Study, *Arch. Path.* **21**:127-164 (Feb.) 1936.

43. Brunschwig, A.; van Prohaska, J.; Clarke, T. H., and Kandel, E. V.: A Secretory Depressant in Gastric Juice of Patients with Pernicious Anemia, *J. Clin. Investigation* **18**:415-422, 1939.

44. Brunschwig, A.; Clarke, T. H.; van Prohaska, J., and Schmitz, R.: A Gastric Secretory Depressant in Extracts of Achlorhydric Carcinomatous Stomachs, *Ann. Surg.* **113**:41-46, 1941.

45. Ivy, A. C., and Gray, J. S.: Enterogastrone, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1937, vol. 5, pp. 405-409.

that the effect of these substances is to stimulate gastric secretion. It is emphasized that neither substance can be expected to give the therapeutic effect of these substances. "Other gastric secretory depressants have been isolated from the urine." Quieley and Lippincott reported that there are inherent protective relations in the stomach which guard against mucosal irritation. All of these experimental studies indicate the complexity of gastric physiology, which in abnormal states is much more even more complex.

Many factors have been suggested as contributing to the production of gastric cancer in human beings. "So little better than give unquestionable indication that extremely factors are of chief importance." In these studies naturally heat came into consideration. The mechanical effect of hot food was studied by Lerche.<sup>46</sup> The importance of diet as a contributory factor and the need for studies in this field was emphasized by the Gastric Cancer Conference.<sup>47</sup> The basis for these studies was established with Singer's<sup>48</sup> early experiments, by which he produced hyperplasia and ulcers in rats. Later work by Pappenheimer and Larimore<sup>49</sup> showed the possible relationship of lesions of the forestomach to dietary deficiency but did not reveal which deficiency was responsible. The recent studies of Morris and Lippincott<sup>50</sup> purported to discover whether there are specific dietary factors on which animals may be maintained a sufficient length of time to produce papillomas or chronic ulcer and allow them to become malignant. In the production of papillomas, amazingly enough, fasting and partial inanition were found to be of greater importance than loss of any one individual dietary substance. Superficial ulcers were also observed during fasting and partial inanition. No malignant lesions were found. A number of observers have pointed out the production of ulcers on a protein deficiency basis.<sup>51</sup> The most important study in this group was done by Weech and Paige,<sup>52</sup> who produced typical ulcers in the

46. Kosaka, T., and Lim, R. K.: Demonstration of the Humeral Agent in Fat Inhibition of Gastric Secretion, *Proc. Soc. Exper. Biol. & Med.* **27**:890-891, 1930.

47. Quieley, J. P.: Enterogastrone-Significant Steps in Development of the Present Conceptions, *Am. J. Digest. Dis.* **8**:363-364, 1941.

48. Friedman, M. H. F., and Sandweiss, D. J.: The Gastric Secretory Depressant in Urine, *Am. J. Digest. Dis.* **8**:366-371, 1941.

49. Grant, R.: Calcium in Gastric Mucus and Regulation of Gastric Acidity, *Am. J. Physiol.* **135**:496-503, 1942.

50. Babkin, B. P.; Hebb, C. O., and Krueger, L.: Changes in the Secretory Activity of the Gastric Glands Resulting from the Application of Acetic Acid Solutions to the Gastric Mucosa, *Quart. J. Exper. Physiol.* **31**:63-77, 1941.

51. Bonné, C.; Hartz, H.; Klerks, J. V.; Postluma, J. H.; Radsma, W., and Tjokronogoro, S. I.: Morphology of Stomach and Gastric Secretion in Malays and Chinese and Different Incidence of Gastric Ulcer Cancer in These Races, *Am. J. Cancer* **33**:265-279, 1938. Footnote 13.

52. Lerche, W.: A Contribution to the Etiology of Cancer of the Esophagus and Stomach, *Surg., Gynec. & Obst.* **23**:42-54, 1916.

53. Singer, C.: The Production of Ulcers of the Stomach in the Rat, *Lancet* **2**:279-281, 1913.

54. Pappenheimer, A. M., and Larimore, L. D.: The Occurrence of Gastric Lesions in Rats, and Their Possible Relation to Dietary Deficiency, *J. Exper. Med.* **40**:719-732, 1924.

55. Morris, H. P., and Lippincott, S. W.: Production of Gastric Lesions in Rats by Fasting, Partial Inanition, and Deficiency of Certain Dietary Constituents, *J. Nat. Cancer Inst.* **2**:459-477, 1942.

56. Hoelzel, F., and DaCosta, E.: Production of Peptic Ulcers in Rats and Mice by Diets Deficient in Protein, *Am. J. Digest. Dis. & Nutrition* **4**:325-331, 1937.

57. Weech, A. A., and Paige, B. H.: Nutritional Edema in Dog: Peptic Ulcer Produced on Low Protein Diet That Leads to Hypoproteinemia and Edema, *Am. J. Path.* **13**:249-256, 1937.



gastric mucosa of dogs. There are also the many studies of Roffo<sup>58</sup>; these are extremely difficult to evaluate. By various experiments in which he fed irradiated cholesterol he produced widespread changes in the glandular epithelium. Some of the lesions showed dilated and atypical glands growing down into the muscularis. There were no metastases, and none of the growths went through the serosal coat. Specific vitamin deficiencies have been tested. The views of Wolbach and Howe<sup>5</sup> are in conflict with those of Howes and Vivier<sup>59</sup>; the latter believed that the bringing on of secondary deficiencies produced the lesion. Howes and Vivier produced the less common glandular lesions, but so far they have been nonmalignant. Functionally, a histamine-fast achlorhydria on a basis of thiamine deficiency has been shown to occur along with a macrocytic anemia in some patients.<sup>60</sup>

In discussing the many dietary experiments and the explanations which could be derived therefrom, the element of how irreparable the lesions produced really are is of first importance. If the mucosal changes will revert to normal after resumption of a complete diet they cannot be considered malignant. This reversion was the common finding in most experiments. Yet the importance of changes which have been produced in the glandular stomach must not be overlooked. If they can be maintained through many years by the technic of partial inanition, a condition more closely approaching the human deficiency state would be approached. The time is now at hand when it would be profitable to use the type of experiments which produce glandular mucosal lesions and to keep the animals alive for a long period by intermittent feedings continued for too short a time to allow the mucosa to recover.

*Alcohol.*—The role of chronic alcoholism in the production of chronic gastritis is still a matter of speculation. Berry<sup>61</sup> has shown that attempts to produce chronic alcoholic gastritis have had inconclusive results. A well controlled observation was made by Hirsch, who demonstrated petechiae in the mucosa but no true inflammatory cell infiltration. Gray and Schindler's<sup>62</sup> observations of chronic alcoholic addicts point up those of Berry. They showed that about one half of the subjects had no important gastric changes. In the remainder the changes were superficial gastritis and atrophic gastritis or a combination of the two. Gray and Schindler could show no correlation between the amount of alcoholic intake and the extent of the gastritis. According to these observations it should be possible to produce experimental chronic inflammatory changes in the gastric mucosa. If such experiments are performed, the importance of accessory dietary factors should not again be underestimated.

*Bacteria, Bacterial Products, Viruses, Allergy.*—Cramer<sup>63</sup> did as nearly similar dietary experiments as possible a number of years apart. In one instance papil-

58. Roffo, A. H.: (a) Bildung von Geschwüren und bösartigen Geschwülste im Verdauungsapparat durch Einführung von Nahrung mit bestrahlten Cholesterin, *Ztschr. f. Krebsforsch.* **47**:473-497, 1938; (b) Producción de úlceras y tumores malignos en el aparato digestivo por la ingestión de alimentos con colesteroína irradiada, *Bol. Inst. de med. exper. para el estud. y trat. d. cáncer* **14**:589-655, 1937.

59. Howes, E. L., and Vivier, P. J.: The Relation of Diet to the Occurrence of Gastric Lesions in the Rat, *Am. J. Path.* **12**:689-700, 1936.

60. Williams, R. D.; Mason, H. L.; Smith, B. F., and Wilder, R. M.: Induced Thiamine (Vitamin B<sub>1</sub>) Deficiency and Thiamine Requirement of Man, *Arch. Int. Med.* **69**:721-738 (May) 1942.

61. Berry, L. H.: Chronic Alcoholic Gastritis: Evaluation of the Concept with Gastroscopic Studies in One Hundred Cases, *J. A. M. A.* **117**:2233-2236 (Dec. 27) 1941.

62. Gray, S., and Schindler, R.: The Gastric Mucosa of Chronic Alcoholic Addicts: A Gastroscopic Study, *J. A. M. A.* **117**:1005-1011 (Sept. 20) 1941.

63. Cramer, W.: Papillomatosis in the Fore-stomach of the Rat and Its Bearing on the Work of Fibiger, *Am. J. Cancer* **31**:537-555, 1937.

There were probably no lesions in the rat, but it has been suggested a virus as causative agent. One may suspect a virus as etiologic for almost any lesion, but proof is difficult.

It is known that the stomach is highly resistant to the usual bacterial agents. The specific resistance to tubercle bacilli and of syphilis is known. The mechanism of the persistent achylia, which follows many pyogenic infections is not clear. Thomsen<sup>66</sup> noted that this was present even before the gastritis developed. There is a paucity of experimental studies which utilize the infectious factor. Hanke<sup>67</sup> reported an erosive gastritis produced by diphtheria toxin.

The question of allergy as the initiating factor in chronic gastritis is occasionally considered. Harten, Gray, Livingston and Walzer<sup>68</sup> have shown the unquestionable absorption of unaltered protein from the digestive tract, and this may have a bearing on the production of gastric ulcer. It is possible to produce a very destructive ulcer in the stomach by using the Arthus phenomenon.<sup>69</sup>

Finally, there is the question of the carcinogens in the production of gastric cancer.<sup>70</sup> This subject was thoroughly reviewed up to 1940 by Klein and Palmer.<sup>5</sup> They concluded at that time that there had been no well defined adenocarcinomas of the stomach produced by the application of carcinogens. Since then Stewart and Lorenz<sup>70</sup> have reported that by direct injection of a powerful carcinogen (dibenzanthracene, methylcholanthrene) adenocarcinomas of the glandular stomach of mice have been produced (fig. 1). Until this had been accomplished, there was considerable doubt as to whether or not cancer of the stomach could be produced with any regularity in lower species. While the numbers in which neoplasms were produced are still not great (Stewart and Lorenz<sup>70</sup> found 44 adenomas and 8 adenocarcinomas in 293 mice) they are enough to suggest that the method may be applicable to larger animals. The control series did not show any spontaneous

64. Broders, A. C.: Tuberculosis of the Stomach, with Report of a Case of Multiple Tuberculous Ulcers, Surg., Gynec. & Obst. **25**:490-501, 1917.

65. Eusterman, G. B.: Gastric Syphilis: Observations Based on Ninety-Three Cases, J. A. M. A. **96**:173-179 (Jan. 17) 1931.

66. Thomsen, E.: (a) Etudes sur l'achylie neurogène et cellulaire, Acta med. Scandinav. **61**:377-433, 1925; (b) Clinical and Experimental Studies of Gastric Juice, *ibid.* **82**:311-328, 1934.

67. Hanke, H.: Ueber experimentelle erosive (peptische) Gastritis durch Diphtheriotoxin. Beitr. z. path. Anat. u. z. allg. Path. **95**:391-402, 1935.

68. Harten, M.; Gray, I.; Livingston, S., and Walzer, M.: Studies in Absorption of Undigested Protein: II. Absorption from the Stomach and Esophagus, J. Lab. & Clin. Med. **27**:54-58, 1941.

69. At the beginning of the discussion of this subject it is necessary to take note that many previous experimenters probably produced squamous carcinoma of the forestomach and even early adenocarcinoma of the glandular portion. However, their reports were not clear enough to establish this absolutely and caused a deal of discussion about the criteria for admitting a particular experimental lesion to the ranks of a true adenocarcinoma. It would seem reasonable enough to accept the criteria that are usually used in human pathology and certain others useful in experimental work. These are given by Klein and Palmer<sup>5</sup> as the irreversibility of the neoplastic properties of a lesion, in the absence of the extrinsic factor initiating the cellular change, and evidence to indicate a causal relation of the experimental procedure to produce the tumor. According to Mallory,<sup>22</sup> it looks as if the cytologic diagnosis of gastric cancer may be made at an extremely early stage, and an attempt should be made to apply this early cytologic picture to experimental work. Adenocarcinoma of the stomach is a relatively slow growing neoplasm; and once the lesion is recognized, time for it to progress following any experimental procedure will be allowed. If necessary, biopsy or gastroscopic examination rather than the usual autopsy should be performed on experimental animals to follow the course of the disease.

70. Stewart, H. L., and Lorenz, E.: Adenocarcinoma of the Pyloric Stomach and Other Gastric Neoplasms Induced in Mice by Carcinogenic Hydrocarbons, J. Nat. Cancer Inst. **3**:175-189, 1942.

adenocarcinomas. This method of inducing adenocarcinoma would be extremely useful in early diagnostic work. Its importance lies in the proof that the application of a foreign substance to the gastric mucosa can produce an adenocarcinoma. Added interest derives from the finding that such adenocarcinomas possess little, if any, peptic activity.<sup>71</sup> It is not likely that the production of an adenocarcinoma



Fig. 1.—*A*, section through an adenocarcinoma of the glandular portion of the stomach. There are invasion and destruction of muscularis, formation of a tumor nodule on the peritoneal surface, and an area of ulceration ( $\times 9.6$ ). *B*, sections from the peritoneal nodule of the adenocarcinoma shown in *A* ( $\times 156$ ). (From Stewart and Lorenz.<sup>70</sup>)

71. Greenstein, J. P., and Stewart, H. L.: Note on the Enzymatic Activity of the Transplanted Adenocarcinoma of the Mouse Stomach, *J. Nat. Cancer Inst.* 2:631-633, 1942.

in the stomach by the use of such known environmental carcinogens would be applicable to our reasoning on the causation of gastric cancer in man. On the other hand, once an adenocarcinoma is so produced it provides the usual possibilities for transplantation studies.

#### EXPERIMENTAL APPROACHES

It was hoped at the outset of this analysis that perhaps some new aspects might be discerned for use in the experimental solution of the problem of human gastric cancer. The considerations that have been discussed were essential to arriving at a sound background for a study of causal genesis.

From the standpoint of its occurrence in the human disease, it must be experimentally proved whether chronic gastritis is actually a precursor, a cause or simply an associated state (fig. 2). It is realized that the question of this relationship still certainly remains an open one. In reviewing the literature one cannot escape being impressed by the studies which point out a positive association between the two states. Evidence opposing the idea might be just as fruitful, from the experimental point of view, as affirmative evidence. If the association is proved, it is then necessary to think of why the neoplasm arises at a particular spot in a generally

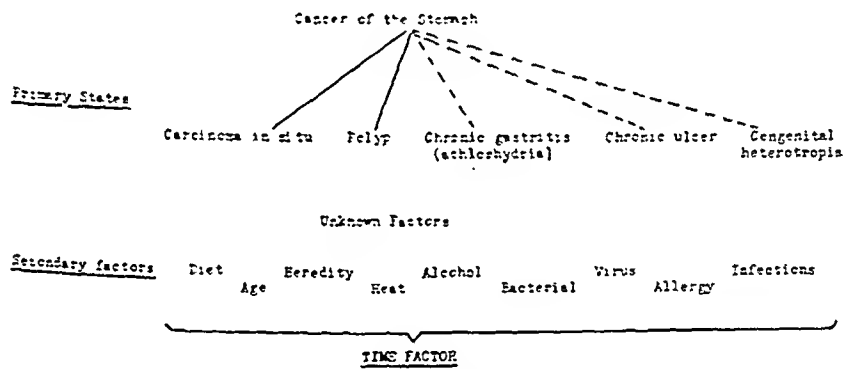


Fig. 2.—Causal genesis of cancer of the stomach. The secondary factors represent points for experimental attacks. Broken lines indicate that the relationship between the conditions named and cancer of the stomach is still unproved.

damaged mucosa. This brings to mind that there may well be "secondary" factors which are completely unknown and unconsidered (fig. 2). These factors one must seek among those of the environment which are already known. An atrophic gastric lesion and an unexplained gastric anacidity have been discovered in monkeys.<sup>72</sup> The anacidity occurs with approximately the same frequency as in man.<sup>73</sup> Both conditions should be extensively studied as to their causation, clinical manifestations and possible connection with cancer. Old animals should be culled over for a clinical and pathologic diagnosis of chronic atrophic gastritis. Given an animal with atrophic gastritis or a damaged mucosa, the environmental factors thought to produce cancer in man should then be brought to bear. The problem of the transition from chronic gastric ulcer to gastric cancer should be settled once and for all. It is understood that the necessary environmental agents will be used in powerful concentration once the chronic ulcers are produced.

72. Schnedorf, J. S., and Ivy, A. C.: The Incidence and Permanence of Unexplained Gastric Anacidity in the Rhesus Monkey After Histamine and Mecholyl, with Hematologic Studies, *Am. J. Digest. Dis. & Nutrition* 4:429-432, 1937.

73. Pollard, W. S., and Bloomfield, A. L.: Diagnostic Value of Determinations of Pepsin in Gastric Juice, *J. Clin. Investigation* 9:107-113, 1930.

The dietary studies which are yielding information should be continued as long time experiments. The much neglected bacterial and virus approach should be repeated or attempted with the modern methods now available. The production of adenocarcinoma by application of effective carcinogens offers real clinical aid to investigation of the early phases and progress of the disease.

The experimentalist has generally remained unappreciative of the usefulness of common laboratory procedures which are widely available for study of the human disease: biopsy, gastroscopy and determinations of free and combined hydrochloric acid, pepsin and rennin and enterogastrone. By their application one could follow more capably the experiment's course and avoid the killing of the animals. Lim<sup>15c</sup> has worked on histogenic detail, and Ferguson<sup>15</sup> has confirmed previous work on regrowth following acute trauma. There is dire need for similar studies after chronic trauma by use of dietary variables and addition of damaging agents. There is always use for morphologic evidence correlating changes in the mucous membranes away from the site of a tumor with studies of the type of tumor and clinical studies. Taking multiple sections, even in questionable cases, may lead to fuller knowledge of the earlier phases. Fundamental anatomic and physiologic observations on older animals are needed. If there is a true difference between the gastritis which accompanies cancer and that associated with pernicious anemia, the distinction should be worked out.

#### SUMMARY

The belief is coming to be accepted that long time factors are involved in the production of human gastric cancer, and it is assumed that these time factors will have to be duplicated experimentally. It is clear, too, that there is a better chance of producing gastric cancer with the environmental agents considered to be responsible in man if these agents are used to simulate those conditions of the gastric mucosa most commonly found associated with human gastric cancer, i. e., polyp, chronic gastritis and ulcer. Spontaneous achlorhydria and atrophic gastritis in monkeys are known, and polyps have been produced in rats by dietary deficiency. Morphologic and detailed functional data may now be secured without killing the animal. These ideas lend hope for a closer grasp of the causation of human gastric cancer.

National Institute of Health.

# PATHOLOGY OF CARCINOMA OF THE STOMACH

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When such a large and controversial subject as the pathology of carcinoma of the stomach is compressed within the confines of a short essay, the writer must of necessity curtail discussion of disputed topics and delete everything which does not seem to be of paramount importance. As a result of this policy the following account deals only with those phases of the subject which can be regarded as of importance in diagnosis and treatment and expresses chiefly the personal views and experience of the writer. Practically no mention of other authors is made in the body of the text, but a few selected references are appended. I recommend the fine monograph of Konjetzny and in particular that of Gutmann, Bertrand and Péristiany, which are mines of information. The material on which this article is based consists of 225 resected gastric carcinomas and 185 autopsies, 42 of which were made on persons whose stomachs had previously been resected.

## THE PRECANCEROUS STOMACH

It would be of the utmost importance if it were possible to know and recognize exactly what anatomic and physicochemical changes take place in the stomach preceding the development of cancer, but as yet little definite information exists. A few facts are generally recognized. A small number of cancers develop in adenomatous polyps, and it seems proper to regard these benign tumors as precancerous hyperplasias. But they are rare and must account for very few gastric cancers.

The relationship of cancer to chronic peptic ulcer of the stomach is a much debated one. The writer is one of those who believe that cancers can form in the margin of a preexisting chronic ulcer and that such tumors differ from ulcerated cancers. In the five year period from 1937 through 1941, 13.4 per cent (11 of 82 cases) of the gastric cancers resected had developed at the margins of preexisting ulcers. Probably a larger percentage than this are preceded by ulcers. In advanced stages it is no longer possible to recognize the peptic ulcer since it has become overgrown by cancer. In addition to this, peptic ulcers are sometimes found in stomachs which have cancers in other parts. Whatever one may believe about the relationship, it can be regarded as certain that whatever factors lead to the development of peptic ulcers are at least not unfavorable to the development of gastric cancer.

It is popular to believe that cancer never develops in a normal mucous membrane but always in a stomach which has been chronically inflamed. The information existing about this subject is exceedingly nebulous and conflicting. This is so not only because the stomach is not an organ which lends itself easily to biopsy, so that very few histologic observations have been made on the gastric mucosa before the development of cancer, but because the criteria of what constitutes gastritis are not established, but vary according to the personal prejudices of different observers. If one strips away the hopelessly confusing use of the adjectives "atrophic" and "hypertrophic" and retains only descriptive phrases

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and sentences, it appears that in some persons the mucous membrane of the stomach suffers a change which tends to increase the mucous cells of its glands at the expense of the chief and parietal cells (fig. 1). The transformed glands tend to approximate the appearance of intestinal glands and in addition may show cellular irregularities. Such changes may be associated with thickening or thinning of the gastric mucosa, and inflammatory cells may vary in their number and kind or be absent. If thickening is exaggerated it may even be polypoid in nature. Except in extreme cases this change is not uniform throughout the stomach, but patchy. In this respect it resembles the patchy hyperplasia of mammary duct cells in the subclinical form of chronic cystic disease of the breast. Stomachs with



Fig. 1.—Chronic gastritis. There has been a complete disappearance of chief and parietal cells with replacement by columnar cells of mucus-secreting type, so that the gastric mucosa here looks like intestinal mucosa (see figs. 2 and 8).

cancers in them not infrequently show this type of mucous membrane, and there is some reason to believe that it may be regarded as a potential precancerous change. But I should like to testify that I have been unable to predict this microscopic change from the gastroscopic appearance or the postoperative gross aspect of the gastric mucosa. It has been pointed out that this type of mucous membrane is regularly found in pernicious anemia and that the gastric cancer rate in pernicious anemia is higher than its expectancy in the population. But too much importance should not be attached to this. There are 225 resected gastric cancers in the group discussed in this paper, and only 1 patient was known to have had

pernicious anemia. As Jenner pointed out, the important lesion is the disappearance of the chief and parietal cells and their replacement by mucous cells, which may lead either to pernicious anemia or to gastric carcinoma. If this is true one need not be surprised to find both pernicious anemia and gastric carcinoma coinciding in the same individual.

It should be emphasized that it is really entirely unknown and unproved whether or not there is a sequential relationship between this so-called chronic gastritis with its glandular changes and gastric carcinoma.

#### THE ONSET OF CANCER

The great majority of gastric carcinomas are derived from the mucus-secreting cells of the mucosa. An insignificant number come from heterotopic pancreatic duct and intestinal mucous cells in the stomach, and a few carcinoids develop from the basigranular cells of the gastric mucosa. The pyloric end of the stomach is most frequently affected, and more tumors begin on the superior half of the stomach than on the inferior, but no part is exempt, including the fundus and the cardia. When cancer cells are grown from an explant in vitro in a uniform medium, they tend to spread from it in all directions at a relatively uniform speed, so that if nothing interferes a sphere is formed with the explant in the center. When cancer grows from a focal point or points in the stomach, factors about which little or nothing is known operate to inhibit the growth in some directions and favor it in others. Thus one finds some cancers projecting into the lumen while there is but little penetration into the wall, others penetrating through the wall directly without projection and a third group in which growth is chiefly along the wall paralleling the surface. Some cancers are associated with ulceration from the start; in others it may come either as a late manifestation and still others may never ulcerate. The formation of fibrous tissue is another variable which has an important effect on the appearance of the cancer. A detailed description of the gross forms of cancer appears in a later section. Here it seems important to stress the variations in directional growth in different carcinomas and to repeat the warning that one may look for cancers in stomachs with gastritis, peptic ulcer or adenomatous polyps.

#### HISTOPATHOLOGY OF GASTRIC CARCINOMA

It has already been stated that almost all gastric carcinomas are derived from the mucus-secreting cells of the stomach. When these cells proliferate as cancers the cells may produce relatively well formed tubules lined by columnar cells with basally oriented nuclei, or they may appear as solitary rounded units, non-coherent, undifferentiated, without secretory activity and apparently expending all cellular energy in reproduction (fig. 2). Between these two extremes all gradations exist. Functional activity may be on an orderly basis with mucus formed in the luminal pole of a cell lining a cancer tubule and subsequently excreted into the lumen of that tubule, or it may be atypical in either one of two different ways. The mucus may be secreted in great quantities, so that the cells producing it may appear inundated by it, or otherwise undifferentiated rounded cells may secrete mucin, which remains within the cell body distending it and flattening the nucleus against the cell capsule, thus forming a so-called signet ring cell. These aberrations of growth are quite likely to appear in all of the hitherto described variations in different parts of the same tumor. It is quite rare to find a carcinoma which is relatively well differentiated, so that it displays some secretory activity in all of its ramifications, and equally rare to encounter a completely



undifferentiated one. Usually the tumors vary in different parts. In my experience attempts to predict the degree of malignancy, the rate of growth and the probable success or failure of surgical treatment based on cellular differentiation alone are of very little value when applied to an individual case, although some small percentage of difference may appear in large groups, testifying to the general truth of the principle that tumors composed of cells which devote most of their energies to reproductive activities are apt to be faster growing and more rapidly invasive than those composed of cells which divide their time between reproduction and functional activities.



Fig. 2.—Carcinoma of the stomach, superficial spreading type. The carcinoma cells have destroyed and replaced all of the mucosa except a few deeply placed glands lined with columnar cells (see figs. 1 and 8).

The microscope can best be employed in the study of gastric neoplasms first for determining whether or not a lesion is a carcinoma. If it is a carcinoma the direction and extent of the spread and the relation of tumor cells to blood and lymphatic vessels and lymph nodes furnish far more valuable information than attempts to determine the percentage variation of differentiated and undifferentiated cells. The most highly differentiated tumor can kill just as effectively as an anaplastic growth if it is not all removed. Moreover, I feel it is not only a waste of time but also deceptive to attach histologically descriptive adjectives and prefixes to gastric carcinomas. Who is to determine what proportion of tubules a

carcinoma shall form before it is to be called adenocarcinoma? How much mucin must be secreted in order that a tumor shall be called a colloid or mucoid carcinoma? Far more valuable is it to describe the gross forms of cancer, since it is important for diagnostic procedures to know these and since they also have some bearing on prognosis. They will be described in the next section.

The growth of carcinoma in the stomach is accompanied by certain phenomena worth noting. As the tumor cells multiply there is always a fibrous framework formed, which furnishes a support for them. In that portion of the tumor which projects into the lumen, this process is usually not very conspicuous, but where the tumor penetrates the gastric wall the amount of fibrous tissue is much greater. It thickens the various coats and separates the muscle bundles, and the process of fibrosis extends well out beyond the periphery of the tumor. It is not, however, any greater, and is sometimes less, than the fibrosis of the gastric wall about a peptic ulcer. In the linitis plastica type of gastric carcinoma, fibrosis of the gastric wall is paramount, and the widely scattered cancer cells may be difficult to recognize. If, as frequently occurs, the carcinoma approaches or actually involves the pylorus, the ring may be greatly narrowed and the lumen constricted by this fibrosis.

The smooth muscle coats may eventually be destroyed by cancerous growth, a process which can occur even without ulceration. But long before destruction occurs the muscle is thickened, not only by the interposition of fibrous tissue between the bundles but by an actual hypertrophy. This can occur even in the absence of both pylorospasm and pyloric obstruction. The same process occurs in peptic ulcer.

Finally, it should be noted that in the presence of cancer the gastric mucosa is generally abnormal and disturbed. An inflammatory cell infiltration is usually present even if there is no ulceration, and dilatation and engorgement of the capillaries account for the reddening which is so common. Except in the rare instance of a carcinoma developing on the basis of a complete mucosal atrophy, some acid-secreting cells are present and functioning. Mucus-secreting cells are always present and active, and their number may be increased at the expense of the chief and parietal cells, so that the appearance of the gastric mucosa sometimes approximates that of intestinal mucosa (fig. 1). But this is by no means constant, and many times the gastric mucosa appears unchanged except for inflammation.

#### THE GROSS TYPES OF GASTRIC CARCINOMA

In the preceding section, the microscopic appearance and growth characteristics of carcinoma have been described in such fashion that the clinically more important gross forms of cancer may be better understood. These will be described under four main heads: fungating carcinoma, ulcerated carcinoma, spreading carcinoma and carcinoma of no special type.

*A: Fungating Carcinoma.*—In this type growth is principally into the lumen, with delayed and restrained penetration into and along the stomach wall. The portion in the lumen is large and often like a cauliflower. It produces a large filling defect with not a great deal of thickening and deformity of the stomach wall until rather late in the course of the disease (fig. 3). Many but by no means all tumors of this type tend to form partly differentiated tubules. The growth becomes superficially eroded on the surface, but extensive and destructive ulceration of the projecting tumor producing a niche in the filling defect is not very common. It is unfortunate that these fungating tumors form only about 10 per cent of all gastric cancers, because as a class they metastasize slowly, and the rate of five year cures following resection is better than 50 per cent.

*B: Ulcerated Cancer.*—A description of the ulcerated cancers is not as simple as that of the fungating tumors; first one must distinguish primary ulcerated tumors from other types which undergo ulceration as a secondary phenomenon; next, the primary ulcerated cancers which are ulcerated from the beginning from those which form in the margins of preexisting peptic ulcers, and, finally, the ulcers which occur in superficial spreading carcinoma from those which occur in deeply penetrating cancers. Most of these can be differentiated on the basis of gross structure, but with the last group differentiation requires the assistance of the microscope.

The ulcerated cancer is recognized now much more frequently than it was twenty years ago, probably because the modern ability to diagnose early cancer is so greatly improved. Ulcerated cancers formed only 11.7 per cent of all the gastric cancers resected at the Presbyterian Hospital in the quinquennial period from

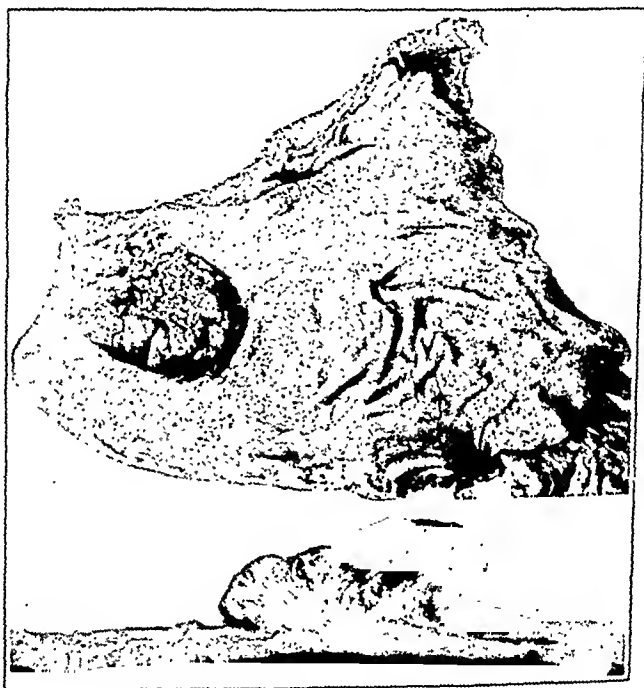


Fig. 3.—Carcinoma of the stomach, fungating type, in a woman aged 68 years. The stomach has been opened along the lesser curvature and the tumor is on the greater curvature with the pylorus at the left. Below is a cross section showing that the tumor has invaded the submucosa but not the muscularis. The mucosa of the stomach appears flattened because it was stretched out and pinned before fixation. There is no atrophy. The patient was well forty-nine months after operation.

1916 through 1920, whereas in the six years from 1936 through 1941 they formed 35.2 per cent.

The primary ulcerated cancer seen on its mucosal aspect is a rounded, rather shallow ulcer, concave like a saucer with shelving edges. It penetrates a short distance into the submucosa or inner muscle coat but does not reach the subserosa. The ulcer bed is covered with an irregular necrotic membrane, and its margins appear irregularly nodular and reddened instead of having the appearance of simple inflamed mucosa as in peptic ulcer (fig. 4). This irregularity may be limited to the immediate vicinity of the ulcer or may extend far outward from it. In advanced stages the area of ulceration may reach a diameter of several centimeters and the

surrounding cancerous mucosa may become elevated as much as 1 cm. or more. The stomach wall beneath the ulcer is thickened by fibrous tissue and by cancer cells which are found in all parts of the ulcer bed and penetrate to the subserosa. Seen from the outside, the region of the cancer is often puckered and scarred and may be reddened by extravasations of blood. If the ulcer has formed in a superficial spreading type of cancer, it has the same mucosal aspect, but the ulceration does not penetrate deeper than the submucosa. Since the submucosa may be greatly thickened by edema and fibrosis, the ulcers can be 3 or 4 mm. deep without reaching the muscularis.

The appearance of a carcinoma which has formed in the margin of a peptic ulcer is different. Seen from the mucosal surface, the ulcer appears deep and



Fig. 4.—Ulcerated carcinoma of the stomach in a woman aged 37 years. The appearance of the ulcer is characteristic. It is shallow with sloping edges and nodular thickening of the surrounding mucosa. The tumor and ulcer are on the lesser curvature with the pylorus at the left. The patient died twenty-eight months after gastrectomy.

punched out, with precipitous walls, and is surrounded by a mucosa which tends to overhang the edges of the defect. There is the same or even greater fibrosis of the gastric wall. The chronic peptic ulcer always penetrates through all of the coats of the stomach, and its base rests on scar tissue outside the gastric wall (fig. 5). If such an ulcer heals it leaves a recognizable scar, since the smooth muscle is not regenerated. When cancer forms at the margins of such an ulcer the cancer cells tend to penetrate through the gastric wall and along it away from the ulcer, but apparently the scar tissue of the ulcer bed is an unfavorable medium for the growth of cancer cells, for they are seldom if ever found in it.

Those who deny that carcinomas ever form in preexisting peptic ulcers explain the appearance just described as the result of complete central destruction of a preexisting carcinoma by the process of ulceration. I do not agree with this



Fig. 5.—Peptic ulcer of the stomach with carcinoma in a man aged 64 years. Characteristic appearance with deep penetration and overhanging mucosal edges on the lesser curvature of the stomach of a man, who had had typical ulcer symptoms for two years. The appearance of the surrounding mucosa does not permit one to suspect the presence of a carcinoma which had penetrated the gastric wall away from the ulcer bed and killed the patient nineteen months after resection.

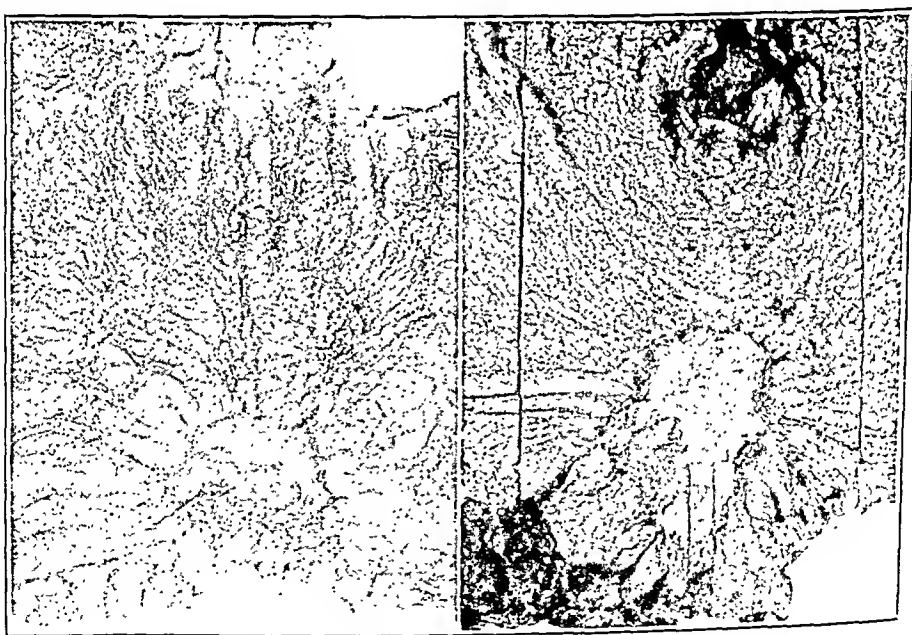


Fig. 6.—Peptic ulcer (left) and ulcerated carcinoma (right). Both lesions are on the lesser curvature at the pylorus. Both are large and shallow and have irregular margins. From the gross appearance it is impossible to know which is which. The patient who had the ulcer and the patient who had the carcinoma are both well, the former ten years and the latter five years after resection.

viewpoint. It is sometimes impossible to distinguish this type of ulcerated cancer from simple peptic ulcer (figs. 5 and 6). One may suspect the presence of cancer

if the surrounding mucosa is irregularly nodular with uneven elevations, particularly if this change extends outward for an appreciable distance from the margin of the ulcer, but there are no reliable criteria which will enable one in every case to distinguish between peptic ulcer with and without cancer. It is also impossible to tell by inspection or palpation whether the carcinoma is superficial, spreading outward in the mucosa or submucosa alone, or whether it is a deeply penetrating tumor. It seems useless to speculate on how frequently carcinoma forms at the margins of a peptic ulcer, because it is only in the relatively early stages of the growth that one can feel confident of the relationship. To complete the picture it must also be stated that carcinoma and peptic ulcer can coexist in different parts of the same stomach, and I have even observed in one specimen a duodenal ulcer on one side of the pylorus and a carcinoma on the other.

The ulcerated cancer is relatively more favorable for treatment than is cancer of the stomach in general, even though regional lymph node metastases are found in nearly half the cases. Of 15 patients treated by resection in the quinquennial



Fig. 7.—Linitis plastica type of gastric carcinoma. The stomach has been opened through the anterior wall with the pylorus at the left. The entire gastric wall is thickened by fibrous tissue containing widely scattered cancer cells. The mucosa is intact and free from gastritis.

period from 1935 through 1940, 5 have died of cancer or are alive with evidences of its persistence, and the other 10 are free from evidences of disease from two to over five years after resection. No doubt this is because of relatively early recognition and prompt operation. It should also be noted that postoperative deaths in the cases of ulcerated cancer are no more numerous than deaths following resection for peptic ulcer.

*C: Spreading Cancer.*—There are two forms of cancer in which the tumor spreads chiefly along the gastric wall. One is well known by name but is so rare that few people have seen it. The other is much more common but is less well known because infrequently described. The rare form is linitis plastica, or leather bottle stomach. In this peculiar condition the entire stomach gradually becomes stiffened by fibrous tissue which forms chiefly in the submucosa, muscularis and subserosa. The mucosa remains practically intact (fig. 7). Scattered at wide intervals in the fibrous tissue can be found a few isolated cancer cells almost obscured

by the predominating fibrous tissue. Such tumors are curiosities. I have examined only 1 genuine example (fig. 7), and this was not included in the Presbyterian Hospital series but was sent to me from another hospital.

The other form is quite different and much more important. In this interesting lesion the neoplastic growth starts as usual in the mucosa and spreads in it, usually penetrating the muscularis mucosae but not going deeper into the gastric wall until a wide surface area has been covered. In one stomach 54 sq. cm. of the mucosa and submucosa had been involved without any penetration into the muscularis. In a few tumors of this type the mucosal involvement is not continuous but patchy, with free areas between the patches. Tumors with multiple areas of superficial mucosal involvement and without penetration of the muscularis mucosae or lymphatics are sometimes called cancer in situ, the connotation being that cancer has begun in a number of different areas at the same time. This is



Fig. 8.—Superficial spreading type of gastric carcinoma in a Negro woman 55 years old. Anorexia, loss of weight, nausea and weakness had been noted for six months. There was a considerable reduction in acid secretion, and the roentgenogram revealed a filling defect. The stomach has been opened along the greater curvature with the pylorus at the left. The tumor appears as a thickening of the mucosa in the antrum extending to the pylorus without ulceration or deep penetration (see figs. 1 and 2).

purely a speculation and has not been proved. Superficial spreading cancer (or slowly progressing superficial erosive cancer, as it has been called by Gutmann and Bertrand) as observed in the material from the Presbyterian Hospital is generally associated with peptic ulcer or else includes superficial bowl-shaped ulcer whose bed reaches the submucosa but does not go deeper. The gross characteristics are the same as have already been described for the ulcerated cancers, although often the mucosal irregularities extend farther outward from the ulcer margin than in those tumors which tend to penetrate at once through the gastric wall. In only 3 instances have broad areas of superficial involvement been observed without any ulceration (fig. 8). Although these tumors remain superficial for a

long time, seemingly they penetrate into the lymphatics with ease, for metastases to the nodes along the upper and lower curvatures were found in nearly half the cases. No case of this type was observed in the surgical material at the Presby-

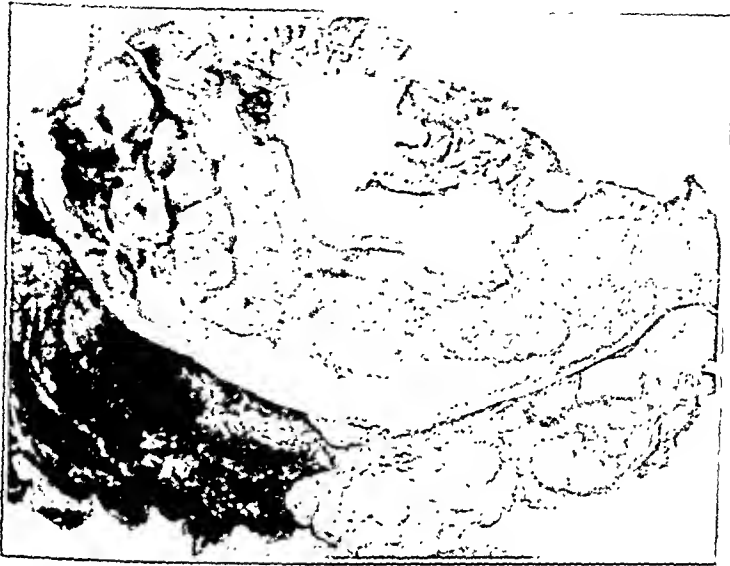


Fig. 9.—Carcinoma of the stomach of no special type in a man aged 42 years. The photograph shows the anterior half of stomach with the pylorus at the right. A very extensive tumor involving most of the gastric wall but with mucosal projections and extragastric invasion (pseudo linitis plastica) with extensive metastases. Death followed operation.



Fig. 10.—Carcinoma of the stomach of no special type in a man aged 65 years. The pylorus is at the left. There is extensive carcinoma surrounding the stomach and involving all coats with production of hourglass deformity and metastases to superior and inferior gastric lymph nodes. The patient died after operation.

terian Hospital before 1937. Since that time there have been 18 cases recorded. Since 15 of these cases were of ulcerated cancer, it may be assumed that the



prognosis for resection with this form of cancer is approximately the same as with ulcerated cancer. In all of the cases from the Presbyterian Hospital the patients survived operation, and so far only 5 of them have died of cancer or are alive with known persisting disease. The rest are alive and apparently well.

*D: Carcinoma of No Special Type.*—Approximately half of the gastric cancers removed in the last five years had grown in such a fashion that it is not possible to assign them with assurance to any of the aforementioned types. In general they were late cancers. Invariably they had penetrated to the subserosa, had extended along the wall and projected into the lumen in varying degrees. Many of them were ulcerated, and the majority involved the complete circumference of the mucosa, especially if they were in the pars pylorica. In some cases growth

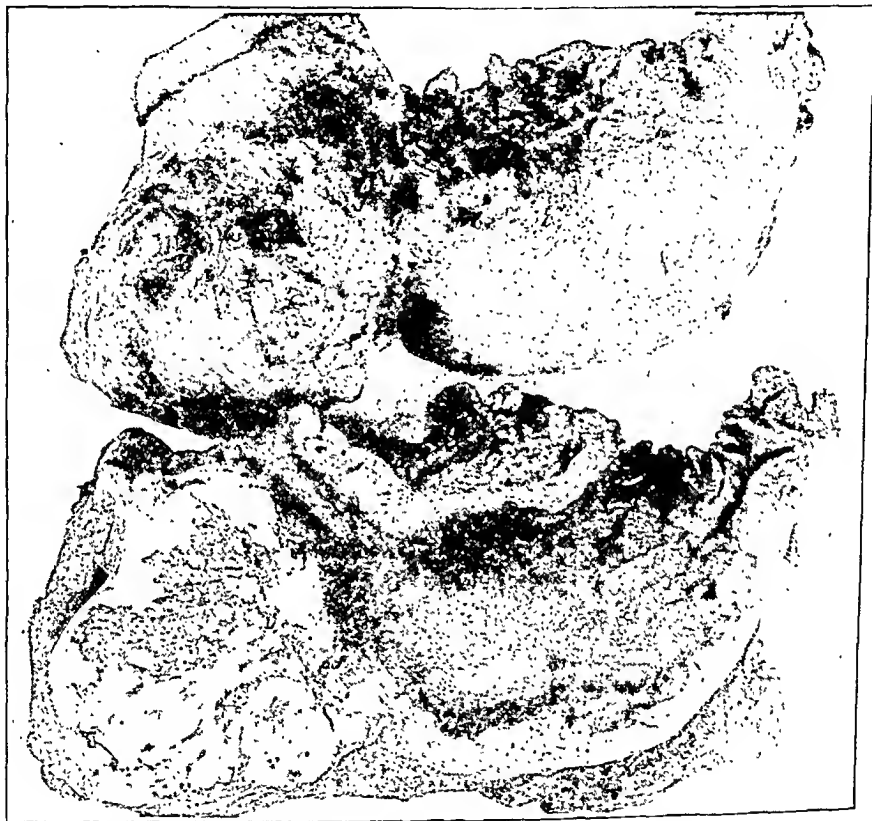


Fig. 11.—Carcinoma of the stomach of no special type in a woman aged 59 years. A large carcinoma involving the entire circumference in the distal end of the stomach showed a tendency to extend outside the gastric wall where it formed a nonadherent mass. Death from cancer occurred four months after operation.

may be exaggerated in one plane so that it simulates a type. There are for instance cancers which approximate the linitis plastica type (fig. 9), but because growth has also taken place in other directions as well as along the stomach they cannot be so called. In fact cancer can produce almost any deformity of the stomach that can be imagined (figs. 10 and 11). This group is not difficult to diagnose, but since most of the tumors are in an advanced stage not many of them are eradicated by gastric resection. In the Presbyterian Hospital group 70 per cent of the patients with cancer of this type had metastases to regional lymph nodes, and the five year symptom-free salvage rate was only 10.6 per cent.

## THE SPREAD AND METASTASIS OF GASTRIC CANCER

Like other carcinomas, gastric cancer spreads to other tissues by direct growth and by metastasis through the lymphatic system and blood vessels. The first method carries it into the duodenum, the esophagus, the gastrophatic and gastrocolic omenta, the pancreas, the diaphragm, the transverse colon and the liver. The lymphatic spread reaches first the lymph nodes along the greater and lesser curvatures and later the other nodes farther afield, and the blood stream carries the tumor cells first to the liver and then to many other parts of the body. A small number of gastric cancers remain localized to the stomach itself. In 143 autopsies in cases of gastric cancer in which resection had not been done 15, or 10.5 per cent, of the tumors had neither metastasized nor extended outside of the stomach wall. Eleven others were limited to the immediate vicinity of the stomach (1 had no metastases but had invaded the duodenum, and 10 showed metastases to gastric lymph nodes only). Thus 26 patients, or 18 per cent, died while their cancers were still in a theoretically operable status. This may be compared with a 30 per cent freedom from metastases to gastric lymph nodes in resected stomachs.

The limits of this paper do not permit an extended analysis of the metastases, but certain facts of interest to the surgeon and the diagnostician must be mentioned. The liver contained metastases in 70, or approximately half, of the cases in which autopsy was performed. The peritoneum, omentum and mesenteries contained metastases in 61 (42.6 per cent) and the lungs and pleuras in 47 (32.8 per cent). Many other organs and tissues received metastases, but in much smaller numbers. Other sites found involved where metastases might become problems of differential diagnosis included: supraclavicular and cervical lymph nodes, 12 cases (8.4 per cent); ovaries, 20 (14 per cent); bones (sternum, vertebrae, rib), 16 (11.2 per cent); pharynx, 4; thyroid, 3; umbilicus and subcutaneous tissues, 1 each, and meninges, 1 (26 brains examined).

In addition to the 143 autopsies on patients who had not had radical operation, there are records of 42 more autopsies on patients on whom gastrectomy had been performed, 34 who died postoperatively and 8 who died after a lapse of 6 or more months. In only 4 of the 34 patients who died postoperatively did the autopsy reveal evidence of a persisting tumor, in 1 locally and in 3 others with metastases. Of the 8 other patients, 1 who had had a fungating tumor showed no evidence of cancer when he died of an enteric infection four years after gastrectomy. In another patient, who had had a fungating tumor resected nearly twenty-three years before his death, a new and independent undifferentiated carcinoma apparently developed in the portion of stomach remaining. Of the other 6 patients, 3 had widespread metastases but no local neoplasm, and the other 3 had local recurrences but no metastases. None of the recurrences was in the duodenal stump.

The method of invasion of the duodenum by gastric carcinoma is of considerable interest. When it occurs the tumor cells may be found in any of the outer coats, which offer no special barrier, but the mucosa is scarcely ever involved for a distance of more than 1 or 2 mm. beyond the pylorus. This fact and the great rarity of primary carcinomas of the first portion of the duodenum have been the cause of much fruitless speculation.

These records suggest that there are many patients with cancer of the stomach who might have been saved by earlier operation and a lowering of operative mortality.

## LESIONS OF THE STOMACH SIMULATING CARCINOMA

The close resemblance between peptic ulcer and ulcerated carcinoma and the fact that carcinoma can start in the margin of a peptic ulcer and that the two

lesions can coexist in different parts of the same stomach have already been discussed, and it is unnecessary to do more than reiterate that no absolutely reliable criteria exist for distinguishing grossly between the two.

Exaggeration and irregularities of the mucosal folds due to vitamin deficiency (fig. 12 *A*) or gastritis may simulate carcinoma, especially if they are found in association with ulcers. Hypertrophy of the pyloric muscle occurring in an adult

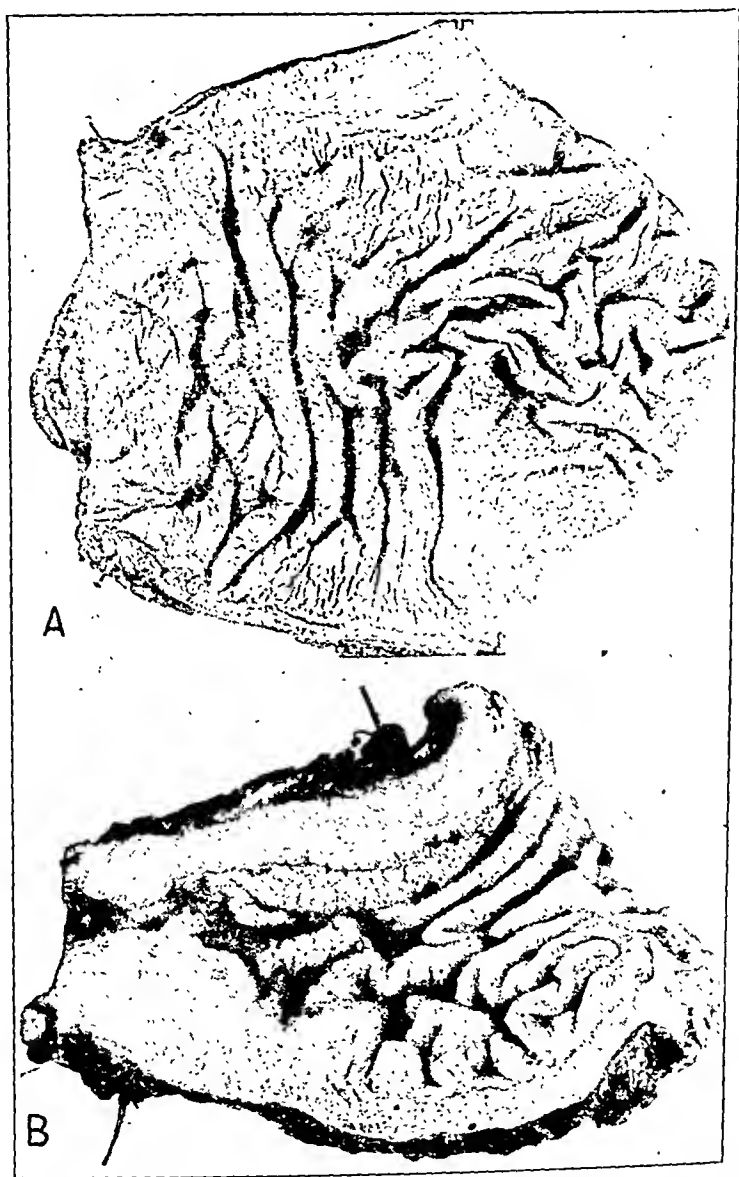


Fig. 12.—*A*, hypertrophy of mucosal folds of the stomach due to nutritional deficiency? A man aged 62 years had suffered for five months with anorexia and semistarvation after extraction of teeth. There was no free hydrochloric acid. A diagnosis of fungating carcinoma was made from the roentgenogram. There was no carcinoma but marked gastritis, exaggeration of mucosal folds and hyperplasia of mucous cells. *B*, Hypertrophy of the pyloric muscle without ulcer or cancer in a Negro aged 45 years. There were rapid loss of weight and low gastric acidity. From the roentgenogram the lesion was diagnosed as probable carcinoma. The photograph shows the posterior half of the stomach with the pylorus at the left. There is marked thickening of the muscularis, especially along the greater curvature. The mucosal folds are thickened, and microscopically there is gastritis with some increase in goblet cells.

(fig. 12 B) and not associated with ulcer may feel like a tumor when the stomach is exposed at operation but not after it has been opened so as to permit inspection of the mucosal surface. The fibrosis, deformity and sometimes ulceration of the stomach associated with syphilis may also simulate carcinoma until microscopic examination proves its absence.

Of the other gastric neoplasms, lymphosarcoma can most easily be confused with carcinoma. Like carcinoma, this neoplasm may manifest itself in a number of different forms. The commonest is the appearance of bulky nodular submucous masses which project into the lumen and simulate fungating cancer. If the overlying mucosa is not ulcerated one may suspect lymphosarcoma, but if it is ulcerated one cannot be sure. In a second form the tumor remains small and invasive with a tendency to ulcerate, which sometimes leads to acute perforation. This type of lymphosarcoma cannot grossly be distinguished from carcinoma. In a third, and rarer, form the tumor tends to extend in the submucosa, producing tremendous thickening of the mucosal folds, and finally may form multiple submucosal plaques. Without the aid of the microscope these forms cannot be diagnosed with any degree of assurance.

The smooth muscle tumors are more easily distinguished because of their smooth outlines, their intramural position with a tendency to produce hourglass tumors and the frequency with which the endogastric projection becomes hollowed out by a sharply defined excavation. The tumors are not as a rule associated with fibrosis or gastritis.

Benign adenomatous polyps can be distinguished from fungating carcinomas because they do not infiltrate through the muscularis mucosae and are not associated with fibrosis. Hence they are freely mobile and do not interfere with peristalsis.

#### SUMMARY

The pathology of gastric cancer has been presented in a summary fashion emphasizing those features which can be considered important in the diagnosis and treatment of this disease. Attention has been focused on the precancerous stomach, the gross forms assumed by early carcinoma, its method of spread and its differentiation from other kinds of gastric lesions.

Dr. Robert C. Horn Jr. did an analysis of the autopsies of gastric carcinomas recorded in the pathology laboratory of the Presbyterian Hospital and Dr. James W. Jobling, Attending Pathologist, gave permission to use them.

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# CHRONIC ATROPHIC GASTRITIS AND CANCER OF THE STOMACH

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The question of the etiologic importance of chronic atrophic gastritis to gastric cancer has been the subject of numerous studies during the past few decades. The association of gastric atrophy with various types of chronic disease has been known for many years. One of the early contributors to the subject, seldom cited today, is Samuel Fenwick.<sup>1</sup> His work comprises two papers on "Atrophy of the Stomach" published in the *Lancet* in 1870 and 1877. These papers alone should be sufficient to arouse suspicion that gastric atrophy is rather more widely found than might be expected by those who would seek to show it a precancerous lesion from the point of view of gastric cancer, merely on the basis of finding morphologic evidence of atrophic gastritis in a large proportion of cancerous stomachs, for Fenwick reported gastric atrophy associated with cancer of many organs. Thus he found gastric atrophy associated with 11 of 15 mammary cancers, 5 of 5 gastric cancers, 3 of 24 uterine cancers, 1 of 3 cancers of the tongue and 1 of 2 rectal cancers, but with none of 11 cancers variously located in the penis, bladder, "groin," glands, bone, skin and lungs. He likewise encountered it in association with chronic cardiac disease, cirrhosis, tuberculosis and nephritis, but to a lesser extent than with cancer in general or with addisonian anemia. It is likely that had Fenwick's material been comprised of multiple large sections his proportion of cases of gastric atrophy would have been considerably increased, since minor changes now recognized as manifestations of gastric atrophy doubtless escaped him. His microscopic investigation was necessarily limited.

To avoid much citation of literature, further reference will be largely restricted to selected more recent papers with direct bearing on the relation of atrophic gastritis to gastric cancer.

Konjetzny in 1913,<sup>2</sup> working with freshly fixed, resected material, postulated a development of cancer of the stomach on an inflammatory basis. He formulated his well known concept of "gastritis hyperplastica atrophicans" and concluded that the greater portion of gastric cancers (about 85 per cent) arose on the basis of chronic gastritis and that the latter constituted a precancerous condition.

Orator,<sup>3</sup> in a series of articles appearing in 1925 based on a study of 700 cases of ulcer and 150 of cancer, noted the close association between the presence of chronic gastritis and its allied intestinal metaplasia and that of gastric carcinoma, and concluded that about 80 per cent of gastric carcinomas arose on a basis of pre-

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1. Fenwick, S.: On Atrophy of the Stomach. *Lancet* 2:78, 1870; 2:1, 39 and 77, 1877.

2. Konjetzny, G. E.: Ueber die Beziehungen des chronischer Gastritis mit ihren Folgeerscheinungen und des chronischen Magenulcus zur Entwicklung des Magenkrebses, *Beitr. z. klin. Chir.* 85:455-519, 1913.

3. Orator, V.: Beiträge zur Magenpathologie. *Virchows Arch. f. path. Anat.* 255:639, 1925; 256:202 and 230, 1925.

cancerous gastritis and the remainder through cancerous transformation of gastric ulcers, i. e. "ulcerocancers." However, he simultaneously admitted that a severe chronic gastritis likewise usually accompanied gastric ulcer and reported the presence of chronic gastritis in association with such diverse conditions as gastric lymphosarcoma, sarcoma, myoma, benign polyps, worms, gastric ptosis, diaphragmatic hernia and severe systemic infections and intoxications. Orator's conclusions were confirmed in most part by the work of Puchert.<sup>4</sup>

Hurst,<sup>5</sup> in a series of articles appearing between 1929 and 1939, reiterated the opinions of the German pathologists as to the pathogenesis of gastric carcinoma on the basis of chronic gastritis and further subscribed to the theory of malignant transformation of chronic gastric ulcers, but stated that these ulcers were secondary to chronic gastritis. He attributed the relatively low incidence of gastric cancer in females to their death from carcinoma of the breast or uterus on an average of fifteen to twenty years before gastric carcinoma commonly develops.

Jenner,<sup>6</sup> assuming from a statistical study of patients with pernicious anemia that there was a relatively high frequency of gastric carcinoma in that group, believed that this high incidence was due not to the presence of pernicious anemia itself but to the chronic atrophic gastritis which is always present in such cases.

Pathologists as a whole have not been universally committed to the views expressed. Thus Haring<sup>7</sup> warned that perhaps Konjetzny had overemphasized the importance of chronic gastritis as an etiologic factor in the pathogenesis of gastric carcinoma and that the histologic picture of chronic gastritis was the end result of many injurious processes acting on the gastric mucosa. He could not agree with Konjetzny that it was specifically related to gastric carcinoma.

Borrmann<sup>8</sup> expressed the opinion that the majority of gastritides associated with gastric carcinoma were catarrhal, interstitial or atrophic and stated that in very early carcinomas he had almost never seen a severe gastritis. He suggested that the gastritis was a result rather than a cause of the cancer.

Hillenbrand<sup>9</sup> regarded a "normal stomach" in old age as a rarity because of the many exogenous and endogenous injuries concomitant with advancing years, and comparing the frequency of so-called chronic atrophic gastritis in the stomachs of people over 50 with the frequency of similar changes in gastric ulcer and cancer, stated: "It is overwhelmingly indicated that it is no more frequent in cancer than in ulcer-free or cancer-free stomachs of older persons."

Wanser,<sup>10</sup> in a recent careful study, was unable to substantiate Konjetzny's contention that chronic gastritis was a precancerous condition. Sternberg<sup>11</sup> and

4. Puchert, H.: Ueber die Magenschleimhaut bei Geschwür und bei Krebs, Virchows Arch. f. path. Anat. **280**:385-404, 1931.

5. Hurst, A. F.: (a) Precursors of Carcinoma of the Stomach (Schorstein Lecture), Lancet **2**:1023-1028, 1929; (b) Clinical Importance of Achlorhydria, Brit. M. J. **2**:665-669, 1934; (c) Cancer of the Alimentary Tract: Pathogenesis and Prophylaxis, Lancet **1**:553-558 and 621-626, 1939.

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10. Wanser, R.: Die banale chronische Gastritis und ihre Beziehungen zum Magenkarzinom, Beitr. z. path. Anat. u. z. allg. Path. **103**:113-156, 1939.

11. Sternberg, C., in discussion on Neugebauer, F.: Die Gastritisfrage, Zentralbl. f. Clin. **58**:1836, 1931.

Westhues<sup>12</sup> have likewise warned against overemphasis on chronic gastritis as a cause of gastric carcinoma.

Tumen and Liberthal<sup>13</sup> in a recent review of the status of chronic gastritis, stated that despite Konjetzny's work many felt that the origin of cancer from gastritis had not been substantiated and suggested that certain of Konjetzny's specimens would not be considered by other pathologists as showing malignant changes. Schindler<sup>14</sup> and his co-workers have shown that some of Konjetzny's findings in resected material might have been artefacts due to the surgical procedure itself.

With the advent of the popularity of gastroscopic examinations, another group of papers has appeared, presenting the endoscopic concept of chronic atrophic gastritis, and again many suggestions have been made as to its role in the pathogenesis of gastric carcinoma. However, as yet we have been unable to discover a fully adequately correlated pathologic study made on gastroscopically diagnosed cases, nor have we had the opportunity to study enough such cases to enable us to draw any conclusions ourselves as to whether the gastroscopic diagnosis can be substantiated pathologically with uniformity.

Fortunately, despite the wide divergence in interpretation of the significance of chronic atrophic gastritis, the microscopic pathologic picture is relatively clearcut and has been accepted at least as a morphologic entity by all workers in this field. It is generally defined as including: (1) varying degrees of atrophy of the mucous membrane; (2) moderate to marked increase in size and number of lymph follicles and interstitial infiltrate; (3) transformation of pyloric and fundus mucous membrane to the so-called intestinal type, and of fundus mucous membrane to a dedifferentiated pyloric type (pyloric gland heterotopia), and (4) an increase in the interglandular connective tissue and a thickening of the muscularis mucosa.

These changes are closely associated with one another and tend to occur as a rule in identical areas of the mucous membrane. The term "chronic atrophic gastritis" is not entirely satisfactory. In its more restricted use it naturally implies inflammation. It is by no means clear that all lesions included under the definition are "inflammatory" in the narrower sense. It is not our purpose, however, to enter into a philosophic discussion of such matters as, for instance, the relation of atrophy of parenchymatous structures and their replacement by diffuse or follicular lymphoid aggregates, a topic which would lead us too far afield.

The conclusions of the group who hold that chronic atrophic gastritis is a precancerous condition were based, presumably, on the concomitant presence of gastritic changes and gastric carcinoma in surgically resected and autopsy material. No exception should be taken to their anatomic findings, for all were competent and expert students, and their observations vary little, if at all, from those of the group holding the opposite view. However, exception can and should be taken to their unwarranted assumption that the mere presence of chronic atrophic gastritis in a large percentage of their cancer specimens proved any etiologic association. There are four distinctly different conclusions possible:

1. Many persons reaching the gastric cancer age have chronic atrophic gastritis.
2. Chronic atrophic gastritis precedes the development of gastric carcinoma.
3. Chronic atrophic gastritis is the direct result of the presence of carcinoma in the stomach.

12. Westhues, H.: Gastritis, München. med. Wchnschr. 79:2061, 1932.

13. Tumen, H. J., and Liberthal, M. M.: Chronic Gastritis: A Review of Its Present Status, Internat. Clin. 2:263-291, 1941.

14. Schindler, R.; Necheles, H., and Gold, R. L.: Surgical Gastritis, Surg., Gynec. & Obst. 69:281-286, 1939.



4. The development of chronic atrophic gastritis is a nonspecific concomitant of many gastric lesions.

The end result, i. e., the pathologic picture in the resected specimen, would be identical in any of these sequences, and therefore the finding of chronic atrophic gastritis in association with gastric cancer in a large percentage of cases is not proof of any one of these four hypotheses to the exclusion of the other three.

If very early carcinoma of the stomach could be proved consistently associated with either the presence or the absence of gastritis, the problem of relationship would be solved. Unfortunately, the material is not at hand for such a study. The reports in the literature on this point are controversial to say the least. No investigator has seen more than the occasional very early gastric cancer.

A logical attack on the problem would seem to be (1) to ascertain the characteristics of a "normal" stomach, (2) to discover what the changes are which may be

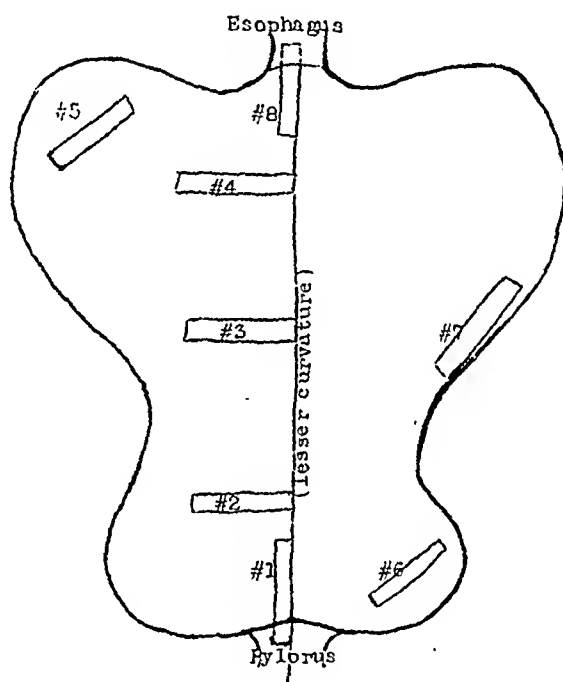


Diagram indicating location of routine blocks taken for study.

expected to occur with advancing age, (3) to study carefully a group of stomachs from people who died of cancer other than cancer of the stomach to determine any "nonspecific" changes in the mucosa associated with the presence of cancer anywhere in the body, and (4) to determine what the mucosal changes are in a group of gastric cancers and whether they differ significantly from the mucosal changes found in association with noncarcinomatous gastric lesions.

#### MATERIAL

The stomachs utilized in this study were for the most part obtained immediately, or within two to three hours at most, after death. It was found that if more time than this elapsed, the material was likely to be unsuitable for study. Many specimens removed within a few minutes after death from patients dying slow deaths were already so digested as to be worthless. Surgically resected material was obtained, as a rule, within five to ten minutes of its removal. The specimens were all carefully opened along the greater curvature, without handling or touching

the mucosa, and fixed flat, without tension, in 4 per cent solution of formaldehyde. After thorough fixation, gross descriptions were recorded, together with data regarding age, sex, state of nutrition, time elapsing between death and fixation, causes of death, nature of gastric contents and any other pertinent facts. At least eight routine sections were taken from each stomach, as indicated in the figure, and such additional sections as seemed indicated for completeness of study. Evidence showed that more sections added nothing of significance.

Five distinct groups of material suitable for study were collected:

Group A consisted of 35 stomachs obtained from premature infants born at from six months' gestation to term and from a few infants who were stillborn at term or who died within a few days of birth.

Group B was made up of 73 "normal" stomachs obtained from persons who had no history or other indication of gastric disease. With few exceptions, these were all from persons who died as a result of trauma or from acute infectious diseases of short duration. This group was augmented by an additional 22 specimens from young subjects who died of electric shock.

Group C included 77 "normal" stomachs obtained from patients who died of nongastric cancers. None of these patients gave any history of gastric symptoms

TABLE 1.—Numerical Distribution of Specimens by Age Groups

Sources of Stomachs by Groups	Distribution by Decades									
	Fetal	Gastric Cancer Ages								
		1	2	3	4	5	6	7	8	9
A. From stillborn infants and infants who died soon after birth .....	23									
B. From "normal" persons.....	..	3	3	5	7	19	16	15	3	2
C. From patients who died of extragastric cancer.....	..	5	5	6	5	11	15	16	7	1
D. From patients with gastric cancer.....	..	..	..	1	1	13	27	22	9	..
E. From patients with noncancerous gastric lesions.....	..	..	..	2	3	5	7	5	2	..

and, so far as could be ascertained, differed from group B only in that they died of cancer after prolonged illnesses.

Group D was composed of 73 gastric carcinomas, the large majority being surgically resected specimens.

Group E was a miscellaneous group of unselected consecutive stomach specimens resected for gastric lesions other than carcinoma, such as gastric ulcer, myoma and sarcoma.

At the risk of reemphasizing well known information but for the purpose of subsequent references to anatomic regions, we are very briefly summarizing the basic normal histologic appearance of the stomach. Three distinctly different mucosal areas are found in the stomach, each with its characteristic glandular components. The cardiac area is a variable zone, extending from a few millimeters to 1.5 cm. from the esophagogastric junction. At this junction the squamous epithelium of the esophagus gives way to a columnar epithelium which lines the gastric mucosal surface. The glands here are compound tubular glands and open directly into the gastric pits, which are lined with a continuation of the surface columnar epithelium. These glands are composed of clear mucus-secreting cells and may normally contain a few parietal cells.

The fundus area, which begins at the margin of the cardiac zone, extends down to the pylorus and comprises about four fifths of the mucosal area of the stomach. The surface and crypts are lined with a continuation of the covering columnar

epithelium. The glands of the fundus are normally of one type, a simple tubular or branched gland which empties into the gastric pits, which are relatively shallow here. These fundus glands are composed largely of the zymogenic, granular chief cells which usually make up the bottom of the tubule and the acidophilic parietal cells which are more numerous in the neck of the gland. In addition, the junction of the crypts and tubules is lined with nongranular mucin-forming cells, termed in this location neck chief cells but probably identical in every respect with the cells of the pyloric glands. This type of cell is normally restricted in the fundus area to the neck of the gland.

The pyloric area begins abruptly at the gastroduodenal junction and extends into the stomach for a distance variously reported as 6 to 7 cm. The surface columnar epithelium is identical with that of the rest of the stomach, but the crypts are deeper, occupying about half the mucosal thickness. The glands, which here are more branched and which show a tendency to coil, are composed almost entirely of clear, mucin-forming cells, identical in appearance with the neck chief cells of the fundus gland. The presence of a few parietal cells is not unusual. In the narrow transitional region between the pyloric and fundus areas, where there is an intermingling of gland types, these clear mucin-forming cells probably may be found normally in the bottoms of some of the fundus glands, but nowhere else may such an occurrence be considered normal.

#### SPECIFIC FEATURES STUDIED

In the study of specimens of tissue from the stomach, some systematic grouping of data is essential, and for this purpose attention was focused on certain ascertainable histologic features. The following factors were noted and tabulated for every individual microscopic section studied.

1. Mucosal thickness. The measurement of mucosal thickness was accomplished with great difficulty and necessarily could not be "exact" owing to the great variation within the individual sections. With considerable care and experience, and with use of a calibrated field, it was possible to ascertain an average mucosal thickness for the individual sections, measuring from the deepest portion of the gland to the outer aspect of the covering epithelium, eliminating the effect of mamillation and irregularities due to rugae.

2. Rugae and mamillation. These were recorded with reference to estimated number, location and degree of prominence.

3. Type of gland and constituent cells. The type of gland present and its degree of development were recorded with reference to the location of the block in the stomach. The type of the component cells of the glands was noted, together with the type and number of abnormal cells present.

4. Lymph follicles and lymphoid collections. These were separately tabulated, lymphoid aggregates with "germinal centers" being designated as follicles and those without such centers as collections. They were classified as to number, size and distribution throughout the mucosa and with relation to rugae. The presence or absence of hyaline collections and giant cells within the lymphoid follicles and collections was noted but was found to have no apparent bearing on the problem, so will not be further mentioned.

5. Leukocytic infiltration. The number and type of cells (including Russell body cells) and their distribution within the mucosa were noted.

6. Muscularis mucosae. Variations in thickness and its involvement by leukocytic infiltration were recorded by location and degree.

7. Interglandular fibrosis. This was tabulated by degree and location.

8. Intestinal metaplasia. Areas characterized by the presence of a columnar surface epithelium with a striated border and scattered goblet cells, together with crypts of Lieberkühn lined with columnar epithelium and occasional goblet cells, and usually with Paneth cells at their bases, were tabulated by degree and extent of the metaplasia and its location.

9. Pyloric gland heterotopia or dedifferentiation of fundus glands. Pyloric type glands of dedifferentiated, mucoid epithelium in the fundus gland area, while usually found in close association with areas of intestinal metaplasia, may also be found in stomachs devoid of metaplasia. Such areas were separately noted.

10. Mucosal cysts. These cysts, characterized by a distended lumen of varying size lined with dedifferentiated mucus-secreting cells, were tabulated as to number and location.

11. Thickness of muscularis.

12. Appearance of the ganglions.

13. Leukocytic plugs occupying the gastric pits.

14. Presence of mucosal edema.

#### OBSERVATIONS

The observations with reference to the aforementioned factors in the five groups of stomachs may be summarized as follows:

*Group A.*—At the sixth month of gestation, the rugae were feebly developed, if present at all. The gastric mucosa varied from 0.2 to 0.4 mm. in thickness, with an average thickness of 0.3 mm. No follicles or lymphoid collections were found, and leukocytic infiltration was totally absent. The pyloric and fundus glands were already differentiated, but the various specialized cells, parietal cells, fundus chief cells and pyloric chief cells might or might not be differentiated. The parietal cells were definitely made out in most cases. Brunner's glands were represented as small buds beginning to pierce the muscularis mucosae of the duodenum.

At the end of the seventh month of gestation, the mucosal thickness was unchanged. The specialized cells were more definitely differentiated, as were the gland areas. The cardiac glands might be seen as they began to develop and apparently started within the stratified squamous epithelium of the esophagus rather than on the gastric side of the gastroesophageal junction, which suggests an origin, at least partial, from the esophagus. Lymphoid follicles and collections were absent, although occasional leukocytes, usually lymphocytes and plasma cells, were seen scattered throughout the mucosa.

By the end of the eighth month of gestation, gastric mucosal measurements varied from 0.3 to 0.7 mm., averaging 0.4 mm. Further stages in the development of cardiac glands from esophageal epithelium might be noted. Brunner's glands in the duodenum were better developed and now lay below a more definitive duodenal muscularis mucosae, and an occasional lymphocytic collection was found in the superficial portion of the duodenal mucosa.

At term the gastric mucosa varied from 0.3 to 0.7 mm., with an average of 0.5 mm. Rugae were but feebly developed, if present at all, and mamillation was absent. The glands were well differentiated, as were the specialized cells. No lymphoid follicles or collections were found, but a few lymphocytes, plasma cells and eosinophilic polymorphonuclear cells were scattered throughout the mucosa in some specimens. Further stages in the development of cardiac glands in the

esophageal mucosa were found and the duodenal glands of Brunner were better developed.

In no specimen examined was there any suggestion of intestinal metaplasia, pyloric gland heterotopia, mucosal cysts or dedifferentiation of specialized cells or of lymphoid follicles. These changes, when present, must be considered to be of postnatal development. The absence of intestinal metaplasia in this group further confirms the studies by Saltzmann,<sup>15</sup> on 7 stillborn babies, by Chuma<sup>16</sup> and more recently by Magnus,<sup>17</sup> on 12 fetal stomachs, and refutes the idea that intestinal metaplasia is congenital in origin, as suggested by Taylor,<sup>18</sup> Stewart<sup>19</sup> and others.

Since the gastric mucosa at term averages but 0.5 mm. in thickness, about half the thickness of adult mucosa, we are safe in assuming that considerable postnatal development of the stomach takes place.

The definite finding of cardiac glands developing within the esophageal squamous epithelium is of importance, especially since Bensley<sup>20</sup> concluded that the "cardiac glands are decadent or retrogressive structures, derived from fundus glands by the disappearance of their more highly specialized cellular constituents," i. e. chief and parietal cells.

*Group B.*—The first decade is represented by 3 specimens from children whose average age was 1 year. The mucosal height varied from 0.6 to 0.9 mm., with an average of 0.7 mm. Rugae were present, low, widely spaced, with some suggestion of mamillation. The glands were well differentiated, as were the specialized cells. The parietal cells had become more numerous in the fundus glands but remained infrequent in the pyloric region. No lymph follicles were present, but an occasional small collection of lymphocytes was noted at the base of the glands along the muscularis mucosae. A few leukocytes, lymphocytes, plasma cells and eosinophils were scattered between the deeper portions of the glands. The glands of Brunner were now definitely developed, and the portion superficial to the muscularis mucosae was moderately infiltrated with lymphocytes, plasma cells and rare eosinophils and showed an occasional lymph follicle. Brunner's glands, which may be said to have developed to the adult phase at this stage, showed no further changes pertinent to this study and will not be further mentioned. Further stages in the development of cardiac glands from squamous esophageal mucosa were present.

By the beginning of the second decade the stomach has attained maturity. In our specimens the gastric mucosa varied from 0.8 to 1.3 mm. and averaged 1.1 mm. in thickness—twice that at birth. Rugae were well developed, and 1 specimen showed mamillation. Parietal cells had become more numerous, the proportionate change being most marked in the pyloric glands, and there appeared to be a definite tendency toward an increase in the parietal cells in the pyloric glands immediately adjacent to the gastroduodenal junction. In 1 specimen examined there were parietal cells in Brunner's glands. Only 1 stomach showed a

15. Saltzmann, F.: Studien über Magenkrebs mit besonderer Berücksichtigung der Schleimhautveränderungen und der im Tumor und an dessen Rand auftretenden Rundzellularinfiltration. Jena, Gustav Fischer, 1913.

16. Chuma, M.: Zur normalen und pathologischen Histologie der Magenschleimhaut, Virchows Arch. f. path. Anat. **247**:236-277, 1923.

17. Magnus, H. A.: Observations on the Presence of Intestinal Epithelium in the Gastric Mucosa, J. Path. & Bact. **44**:389-398, 1937.

18. Taylor, A. L.: Epithelial Heterotopias of the Alimentary Tract, J. Path. & Bact. **30**:415-449, 1927.

19. Stewart, M. J., in Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcer, New York, Oxford University Press, 1929.

20. Bensley, R. R.: The Cardiac Glands of Mammals, Am. J. Anat. **2**:105, 1902.

few small follicles along the muscularis mucosae of the fundus, but all had occasional collections of lymphocytes scattered along the muscularis mucosae with an apparent tendency to be located at the apex of a rugal fold. A few leukocytes, mostly lymphocytes, were seen scattered about the bases of the glands, and a few plasma cells and lymphocytes were found under the covering epithelium.

In the third decade the mucosal thickness varied between 0.8 and 1.4 mm., the average being 1.1 mm. The rugae were well developed, but mamillation was rare. Lymph follicles were rarely seen, and the small ones present were located immediately above the muscularis mucosae. The number of lymphocytic collections varied but there were usually a few of small size, more frequent in the fundus area. Leukocytic infiltration was sparse, consisting of lymphocytes along the bases of the glands, with more plasma cells superficially. Two stomachs, one from a patient who died of glomerulonephritis and the other from a man who committed suicide with a shotgun, showed definite intestinal metaplasia and pyloric gland heterotopia.

In the specimens from persons in the fourth decade, the mucosal thickness varied from 0.8 to 1.5 mm., averaging again 1.1 mm. Rugae continued to be well developed, and mamillation often was present. The glands and specialized cells continued to be well differentiated, although there was an apparent diminution in the number of parietal cells present in the pyloric area. A few follicles and frequent lymphocytic collections, usually small, were often found along the muscularis mucosae. There were usually a few lymphocytes scattered about the deeper portions of the glands and a moderate number of plasma cells and lymphocytes more superficially. Eosinophils and Russell body cells were occasionally seen. However, 1 stomach in this group was completely devoid of infiltrate. Four of the 7 stomachs showed varying degrees of intestinal metaplasia with its associated changes, and 1 additional specimen showed moderate pyloric gland heterotopia in the fundus area.

The special group of 22 stomachs from persons who died instantly of electric shock in the third or fourth decade of life showed no significant morphologic differences from the other stomachs in the same age groups. Four contained areas of intestinal metaplasia, and 7 others had areas of pyloric gland heterotopia, i. e., dedifferentiation of the more specialized fundus type gland to the pyloric type. Despite the fact that all the persons from whom these specimens were taken are known to have eaten a heavy meal two or three hours before death, there is no evidence of "digestive leukocytosis." A quantitative comparison with stomachs of a random group of persons of the same age reveals that the special group not only showed no increase in the amount of leukocytic infiltrate but had actually a slight although not significant decrease. We are therefore inclined to discount the factor of "digestive leukocytosis" as of importance in interpretation of leukocytic infiltration.

In the fifth decade group, as in previous ones, the average mucosal thickness was 1.1 mm., with a variation of 0.6 to 1.6 mm. Rugae continued to be well developed in some specimens, fairly well developed in others and nearly absent in a few. One of the stomachs examined had giant rugae measuring 1 inch (2.5 cm.) in height without accompanying indication of disease, there being no explanation for the condition. Mamillation was equally variable, stomachs with well developed rugae showing well marked mamillation as a rule, but not necessarily so. The glands and cells in general continued to be normally developed and specialized: 3 of the specimens showed many parietal cells in the duodenal mucosa. The number of follicles was inconstant, some stomachs showing no follicles but compensating by having numerous lymphoid collections, while the reverse was as often true. In general, it may be said that follicles and lymphoid collections varied from

A considerable variation in the thickness of the muscularis mucosae is normally found in all stomachs, it being on an average two or three times as thick in the pyloric region as in the fundus and again, as a rule, thicker in the cardia than in the fundus. In the pyloric region smooth muscle extensions of the muscularis mucosae are normally found between the pyloric glands. It is true that in specimens showing marked intestinal metaplasia, pyloric gland heterotopia and heavy infiltrate, the muscularis mucosae may be thickened and fibrosed, but such thickening is not a constant finding and as a criterion for a microscopic diagnosis of chronic atrophic gastritis it is probably not reliable except when considered in association with these other changes. The presence or absence of leukocytic infiltrate in the muscularis mucosae is entirely coincident with the presence or absence of heavy infiltrate in the immediately overlying mucosa and has therefore no independent significance.

Interglandular fibrosis, as would naturally be expected, is found only in association with areas of heavy infiltration, marked mucosal atrophy, intestinal metaplasia and other regressive changes. It is not present in a normal mucosa and does not appear to be of sufficient significance per se to warrant further separate consideration.

Intestinal metaplasia and pyloric gland heterotopia have a similar significance and safely may be said never to be present in a normal stomach. All students agree that such areas are not present at birth. Taylor<sup>18</sup> considered intestinal metaplasia as of congenital origin in some cases, but his material consisted of stomachs resected for cancer or ulcer, and did not include a single normal stomach. Chuma,<sup>16</sup> Magnus,<sup>17</sup> Schmidt<sup>27</sup> and Nicholson<sup>28</sup> all described intestinal metaplasia as a response to injury of the gastric mucosa. Faber and Lange,<sup>29</sup> Konjetzny<sup>30</sup> Hamperl<sup>31</sup> and many others have agreed that areas of intestinal epithelium never occur in stomachs free from the changes of gastritis. Our own material is in complete accord with these conclusions. Our youngest patient with intestinal metaplasia was a 21 year old man. In the fourth decade group, 57 per cent of specimens showed areas of intestinal metaplasia, while in the fifth decade group 68 per cent of them showed such changes. By the time the seventh decade was reached, 80 per cent showed these regressive changes. These foci of intestinal metaplasia when in the fundus are almost always associated with heterotopic pyloric glands and are invariably surrounded by varying amounts of infiltrate and other signs of damage.

Mucosal cysts are probably never found in normal stomachs, since our youngest patient having them was 37 years old. Although they seldom are numerous in the individual stomach, the number of stomachs showing them increases with age until in the sixth decade 81 per cent show at least an occasional cyst. They rarely occur in stomachs not containing intestinal metaplasia or other characteristics of gastritis.

A normal stomach may therefore be defined as a stomach with a mucosal thickness varying not greatly from 1 or 1.1 mm. It may or may not present

27. Schmidt, A.: Untersuchungen über das menschliche Magenepithel unter normalen und pathologischen Verhältnissen, *Virchow's Arch. f. path. Anat.* **143**:477-508, 1896.

28. Nicholson, G. W.: Heteromorphoses (Metaplasia) of Alimentary Tract, *J. Path. & Bact.* **26**:399-417, 1923.

29. Faber, K., and Lange, G.: Die Pathogenese und Aetiologie der chronischen Achylia gastrica, *Ztschr. f. klin. Med.* **66**:247, 1908.

30. Konjetzny, G. E., in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1928, vol. 4.

31. Hamperl, H.: Ueber erworbene Heterotopien ortsfremden Epithels im Magen-Darmtrakt, *Beitr. z. path. Anat. u. z. allg. Path.* **80**:307-335, 1928.

manillation, and rugae are usually present. It may contain a few lymphoid collections and lymph follicles along the muscularis mucosae. Leukocytic infiltrate may vary from slight to moderate without regard to type of cells present as long as the covering mucosa shows no erosion. Intestinal metaplasia, pyloric gland heterotopia, mucosal cysts and interglandular fibrosis are absent.

It is easily seen by table 2 that the incidence of chronic atrophic gastritis rapidly increases with the passage of each decade and that in old age a normal stomach is truly a rarity.

*Group C.*—The group consisted of apparently normal stomachs from patients who died of cancer other than cancer of the stomach. The observations are almost identical with those for the previous group, and for the sake of brevity only such data as appear pertinent will be reported.

In the first decade group the mucosal thickness varied from 0.4 to 1.0 mm., averaging 0.8 mm. The specific glands were well developed and specialized, and there was excellent differentiation of specialized cells. Follicles were absent, and lymphoid collections were few except in 1 specimen from a patient with lymphatic leukemia, a disease considered by many to be neoplastic. As in the previous groups, leukocytic infiltration was slight or more often entirely absent, the only notable exception being in 1 of the specimens from patients with lymphatic leukemia, in which there was a heavy infiltrate just superficial to the muscularis

TABLE 2.—Percentage of Stomachs Showing Chronic Atrophic Gastritis

Group	Percentage by Decades									
	At Birth	1	2	3	4	5	6	7	8	9
A. Stillborn infants and infants who died soon after birth.....	"	0	0	40	71	79	81	87	66	100
B. "Normal" persons.....	"	0	20	66	20	36	66	87	87	100
C. Persons who died of extragastric cancer.....	"	0	20	66	20	36	66	87	87	100
D. Persons with gastric cancer.....	"	0	20	66	20	36	66	87	87	100
E. Persons with noncarcinomatous gastric lesions....	"	0	20	66	20	36	66	87	87	100

mucosae. None of the features of chronic atrophic gastritis are found in this first decade.

In the second decade group the mucosa varied from 0.8 to 1.5 mm., with an average thickness of 1.1 mm. Glandular and cell differentiation were normal. One specimen had parietal cells in the duodenal mucosa. Follicles were absent, lymphoid collections were few and leukocytic infiltrate was slight to absent, except in a stomach from a patient who died of myoblastoma of the heart, which showed an increase in all three, together with such degree of pyloric gland heterotopia that it must be classified as showing chronic atrophic gastritis. Aside from the presence of a few mucosal cysts in 2 other specimens, this group showed nothing further of interest.

The picture in the third decade is similar to that in the previous decade. The mucosal thickness averages 1 mm. One specimen again showed many parietal cells in the duodenal mucosa. However, 2 stomachs showed intestinal metaplasia and 2 others showed significant areas of pyloric gland heterotopia, while a few mucosal cysts were found in 2 instances.

Fourth decade mucosas averaged 0.9 mm. in thickness. Follicles continued to be few. Infiltrate was slight or absent, except in 2 mucosas in which there were a moderate number of cells under the covering epithelium and an occasional Russell body cell. In comparison, decade by decade, with the previous group of stomachs from normal persons, there were consistently fewer follicles, fewer lymphoid collections and less leukocytic infiltrate. One specimen showed intestinal metaplasia.



The mucosal thickness in the fifth decade continued to average 1.0 mm., and glandular and cell differentiation were normal. Parietal cells were again noted in the duodenal mucosa. A quantitative comparison of the specimens for this decade with those of the same decade in the group of normal stomachs from normal patients showed less than half as many follicles and lymphoid collections and significantly less leukocytic infiltrate in this group from patients who died of extragastric cancer. Two specimens showed intestinal metaplasia; 2 in addition showed some glandular dedifferentiation, and 3 showed a few mucosal cysts.

The sixth decade group was a heterogeneous group. Mucosal thickness varied from 0.4 to 1.4 mm. but again averaged 1 mm. Glandular development and differentiation were poor, although the specific cells were as a rule still well differentiated. The individual glands were often spaced by interacinar proliferation of fibrous tissue. Two specimens again showed parietal cells in the duodenal glands. The number of follicles and lymphoid collections continued to be definitely diminished in comparison with the control group, though the difference was not so marked. Leukocytic infiltration was variable, but an average mucosa in this group showed a slight, mostly lymphocytic infiltrate about the bases of the glands and an increased number of cells more superficially, with a preponderance of plasma cells and an occasional Russell body cell. Ten mucosae showed marked intestinal metaplasia; in some the metaplasia was almost complete. There were all stages of pyloric gland heterotopia and epithelial dedifferentiation in the metaplastic mucosae, and in addition 2 other specimens showed marked pyloric gland heterotopia although actual intestinal metaplasia was absent. Mucosal cysts were present in 10 specimens.

The seventh, eighth and ninth decade groups did not differ in any essential factor from the sixth decade group. Thirteen of the seventh decade group showed varying amounts of intestinal metaplasia, while 2 additional specimens had significant amounts of pyloric gland heterotopia and mucosal cysts were found in 13. The eighth decade group contained specimens with intestinal metaplasia, all with mucosal cysts, and the single specimen in the ninth decade showed pyloric gland heterotopia but no actual intestinal metaplasia or cysts.

It is obvious that this group of stomachs was identical in all essentials but one with the previous group of stomachs from apparently normal persons who died relatively sudden deaths, and that difference was in the diminished number of lymph follicles and lymphoid collections and in the lessened amount of leukocytic infiltrate present in these specimens from patients who died of extragastric cancer. From the statistical evaluation to follow, it is also obvious that the difference is beyond the possibility of chance occurrence and that there must be some explanation for the phenomenon. The best explanation is found in a comparison of the nutrition of the two groups of subjects. The patients who died of cancer were as a group definitely malnourished, and there is a proportionate disparity between the nourishment of the two groups and the number of lymphoid aggregates and the leukocytic infiltrate. Furthermore, there is a significant statistical correlation between the nutritional state and the number of lymphoid aggregates and the amount of leukocytic infiltrate within this group. It is therefore probably safe to say that the relative decrease in the number of lymphoid aggregates and the diminution in amount of leukocytic infiltrate were directly related to the poor nutrition of the patients.

The apparent higher incidence of chronic atrophic gastritis at earlier ages in this group was only apparent. The average ages of incidence of chronic atrophic gastritis in groups B and C were practically identical.

*Group D.*—With the exception of a slight but progressive increase in the amount of intestinal metaplasia and pyloric gland heterotopia with increasing age, the decade differences present in the previous groups were entirely absent in this one. Apparently the presence of a carcinoma in the stomach is sufficient to eradicate individual histologic variations usually present and related to differences in age, and this presence converts all stomachs into a surprisingly homogeneous group. In fact, the individual specimens conformed more closely to the mean of this group than in the groups previously considered, with the exception of the specimens from stillborn premature infants.

The thickness of the portions of the mucosa uninvolved by tumor varied from 0.6 mm. to 1.4 mm., with an average of 1 mm., essentially identical with groups B and C. Rugae were, as a rule, well developed, and manillation was usually present away from the immediate vicinity of the tumor, but this was of no significance and was to be expected, as the specimens were nearly all surgical specimens, fixed immediately in solution of formaldehyde while still warm.

As a rule, the dedifferentiation of specialized glands and loss of specialized cells were most marked in the mucosa immediately adjoining the carcinoma. Intestinal metaplasia and pyloric gland heterotopia also were usually more in evidence in the immediate neighborhood of the tumor. However, in some instances the glands immediately adjacent to or surrounded by the tumor retained perfectly their specialized characters and the functional cells maintained an absolutely normal appearance. All gradations between these two extremes may be expected. All but 2 of the 73 specimens in this group showed some degree of intestinal metaplasia or pyloric gland heterotopia, an incidence of 97 per cent.

There was a marked increase in the number of both lymph follicles and lymphoid collections and a proportionate increase in the amount of leukocytic infiltrate present in this group as compared with previous groups. Although they were found in largest amount distributed in the immediate vicinity of the lesion, as a rule the entire gastric mucosa was involved. With regard to the type of cell present, there was a proportionate increase in the number of polymorphonuclears in the neighborhood of the cancers, practically all of which were ulcerated, but in the mucosal areas more distant from the lesion the usual proportion of the various leukocytic components was restored. Russell body cells were often seen in the area immediately around the tumor or even in the mucosal area involved by the tumor. Mucosal cysts were present in 40 of the 73 specimens or in 55 per cent.

This high incidence of chronic atrophic gastritis in association with gastric carcinoma is entirely in accord with the figures of other observers, including Konjetzny, Baker, as quoted by Eusterman,<sup>32</sup> Simpson,<sup>33</sup> Faber,<sup>34</sup> Orator,<sup>3</sup> Hurst<sup>5</sup> and many others.

*Group E.*—This miscellaneous group, composed of specimens resected for gastric lesions other than carcinoma, is included to indicate what the incidence of chronic atrophic gastritis may be expected to be in pathologic conditions of the stomach other than carcinoma. Twenty-one of the 24 specimens, or 88 per cent, showed definite evidence of chronic atrophic gastritis as we have defined this condition. The conclusion suggested by this relatively small number of specimens is further corroborated by the report of Simpson<sup>33</sup> from Guy's Hospital, who found

32. Eusterman, G. B.: The Gastritis Problem: Notes on Histologically Verified Cases. *South. M. J.* 29:685-693, 1936.

33. Simpson, C. K.: Observations on Gastritis. *Guy's Hosp. Rep.* 84:351-362, 1934.

34. Faber, K.: Gastritis and Its Consequences, London, Oxford University Press, 1935.

gastritis in all cases of polyps and peptic ulcers examined, and by that of Konjetzny,<sup>35</sup> who in asserting that too little attention was paid to the chronic gastritis associated with gastric ulcer cited Kalima as finding more or less gastritis in 100 per cent of a large series of cases in which resection was done for gastric ulcer, and stated that he himself had always found chronic gastritis in stomachs resected for chronic duodenal ulcer. Magnus<sup>17</sup> found intestinal metaplasia (used in his very strict interpretation of the term) in 73 per cent of gastric ulcers, while Puhl<sup>36</sup> found intestinal epithelium in all of 140 stomachs removed for gastric ulcer. Orator<sup>3</sup> found an atrophic diffuse gastritis as a rule associated with sarcoma and lymphosarcoma of the stomach and that it was also present in specific infections, in intoxications, in infestation with worms and in gastric tuberculosis.

#### STATISTICAL EVALUATION OF OBSERVATIONS AND CONCLUSIONS

When working with a large number of different biologic factors, each capable of independent variation, it is necessary to test statistically the conclusions drawn from such material to determine whether or not the variations observed are significantly different from chance variations.

The details of the theory and mathematics of these procedures are beyond the scope of this paper. Briefly it may be stated that the significance of an obtained result may be judged by its relation to its probable error. The probable error of the difference between any two quantities is equal to the square root of the sum of the squares of the probable errors of the quantities entering into the difference. When a difference or a constant is less than twice its probable error, it is considered by biometrists to be not significant, since the odds against such a deviation's having occurred by chance are only 4.64 to 1. When a difference or a constant is three or more times its probable error, it is said to be significant, since the probability of the deviation's having happened by chance is less than 1 in 20. All deviations whose probability of chance occurrence is less than 1 in 20 may therefore be considered significant. When a deviation is four times its probable error, the odds against chance occurrence are 142 to 1 and with a deviation five times its probable error, the odds against chance increase to 1,341 to 1 (Pearl<sup>37</sup>).

Similarly, in considering a number of variable biologic characteristics, it is desirable, too, to determine if there is any relationship between their variation, i. e., whether changes in one characteristic influence changes in any other characteristic or whether each is entirely independent of the others. This dependence of variation in one factor on changes in another factor is best indicated by calculating their coefficient of correlation. This coefficient may fall anywhere between 0, which is the result when there is no correlation between the two variables, and either +1 or -1, the latter figures indicating that the correlation is perfect or that for every change in one of the variables there is a definite and constant proportional change in the other. A positive correlation signifies that as one variable increases in value the other variable also increases and vice versa. A negative correlation means that as one variable increases, the other decreases. The significance of the coefficient of correlation is again judged by its relationship to its probable error as stated above.

35. Konjetzny, G. E.: *Chronische Gastritis und Duodenitis als Ursache des Magenduo-denalgewichs*, Beitr. z. path. Anat. u. z. allg. Path. **71**:595, 1923.

36. Puhl, H.: *Ueber die Bedeutung entzündlicher Prozesse für die Entstehung des Ulcus ventriculi et duodeni*, Virchows Arch. f. path. Anat. **261**:1-109, 1926.

37. Pearl, R.: *Introduction to Medical Biometry and Statistics*, ed. 2, Philadelphia, W. B. Saunders Company, 1930.

The following variable factors in this study were tested to determine any correlation with each other:

1. Sex
2. Age by decades
3. State of nutrition or weight
4. Thickness of mucosa
5. The number of lymph follicles and lymphoid collections
6. Amount of leukocytic infiltrate
7. Amount of intestinal metaplasia and pyloric gland heterotopia
8. Presence or absence and number of mucosal cysts

Each factor of each specimen was quantitatively graded, those factors not naturally having numerical values being graded on an artificial scale from 0, indicating complete absence of the factor, to 24, indicating the greatest possible change, such a manipulation being required by the statistical method to be used.

Aside from the higher incidence of gastric cancer in males, 73 per cent of the specimens being from males and but 27 per cent from females, the analysis by sex shows nothing of note. There is no significant difference between the two sexes in mucosal thickness, number of lymphoid aggregates, amount of leukocytic infiltrate or intestinal metaplasia, nor in the number of mucosal cysts.

TABLE 3.—Correlation of Advancing Age with Changes in Other Mucosal Factors

	Group B		Group C		Group D	
	Correlation Coefficient	Significance	Correlation Coefficient	Significance	Correlation Coefficient	Significance
Mucosal thickness.....	$-0.216 \pm 0.056$	No	$-0.141 \pm 0.051$	No	$-0.197 \pm 0.099$	No
Lymphoid aggregates.....	$+0.335 \pm 0.079$	Yes	$+0.251 \pm 0.077$	Yes	$+0.035 \pm 0.079$	No
Leukocytic infiltrate.....	$+0.471 \pm 0.079$	Yes	$+0.375 \pm 0.077$	Yes	$+0.215 \pm 0.079$	No
Intestinal metaplasia.....	$+0.303 \pm 0.079$	Yes	$+0.295 \pm 0.077$	Yes	$+0.312 \pm 0.079$	Yes
Mucosal cysts.....	$+0.110 \pm 0.079$	No	$+0.395 \pm 0.077$	Yes	$-0.050 \pm 0.079$	No
Nutritional state.....	No correlation		No correlation		No correlation	

The study of the relationship of increasing age to mucosal changes shows that with advancing age there is a significant increase in the number of lymphoid aggregates, in the amount of leukocytic infiltrate and in the amount of intestinal metaplasia and glandular dedifferentiation in stomachs not the site of cancer. This effect of age is nullified by the presence of cancer in the stomach, so that only a significant increase in the amount of intestinal metaplasia with increasing age remains. There is no significant correlation between age and the mucosal thickness (beyond the normal growth period of the first decade) in any of the groups, nor is there any significant correlation between the age and the nutritional state. A significant and positive correlation found between the number of cysts and increasing age only in the mucosas of persons dying from extragastric cancer is beyond the possibility of chance, but we have no explanation for it.

Analysis of the effect of variation in the nutrition of the subject on the attributes of the stomach shows but one correlated group of positive facts. There is a highly significant difference in mean body weight between group B persons who died from acute conditions and group C (persons who died of extragastric cancer), indicating a true tendency of patients who die of cancer to be malnourished. There is also a proportionate and equally highly significant diminution in the mean amount of lymphoid aggregates and leukocytic infiltrate present in the group of patients who died of extragastric cancer. This suggestive evidence is corroborated by a significant positive correlation in group C between the state of nutrition and

the amounts of lymphoid aggregate and leukocytic infiltrate present. It may therefore be safely stated that there is a definite tendency toward lessened infiltrate and fewer lymphoid aggregates as the nutritional state declines. No correlation is found between the nutritional state and the mucosal thickness or the amount of metaplasia present in any of the groups.

Study of the relationship of variation of the mucosal thickness to the other characteristics of the mucosa reveals these interesting facts. Despite the fact that the average mucosal thicknesses are essentially identical for all three groups, varying but slightly from 1 mm., there is a highly significant but negative correlation between mucosal thickness and both the amount of leukocytic infiltrate and the amount of intestinal metaplasia in the persons who died acute deaths and those who had cancer of the stomach. An explanation for the lack of correlation between these factors in patients who died of extragastric cancer might lie in the diminished

TABLE 4.—*Correlation of Nutritional State with Mucosal Factors*

	Group B		Group C		Group D	
	Correlation Coefficient	Significance	Correlation Coefficient	Significance	Correlation Coefficient	Significance
Lymphoid aggregates.....	+0.036 ± 0.095	No	+0.258 ± 0.078	Yes	No correlation	
Leukocytic infiltrate.....	-0.041 ± 0.095	No	+0.305 ± 0.078	Yes	No correlation	
Mucosal thickness.....	No correlation		No correlation		No correlation	
Intestinal metaplasia.....	No correlation		No correlation		No correlation	
Average state of nutrition....	15.05 ± 0.444		12.00 ± 0.474			

Difference in average state of nutrition of groups B and C is  $3.95 \pm 0.619$ , significant

TABLE 5.—*Correlation of Mucosal Thickness with Other Factors*

	Group B		Group C		Group D	
	Correlation Coefficient	Significance	Correlation Coefficient	Significance	Correlation Coefficient	Significance
Age (by decades).....	-0.216 ± 0.086	No	-0.141 ± 0.081	No	-0.197 ± 0.099	No
Lymphoid aggregates.....	-0.092 ± 0.081	No	-0.070 ± 0.081	No	-0.167 ± 0.084	No
Leukocytic infiltrate.....	-0.283 ± 0.081	Yes	+0.032 ± 0.084	No	-0.445 ± 0.084	Yes
Intestinal metaplasia.....	-0.493 ± 0.081	Yes	-0.198 ± 0.084	No	-0.429 ± 0.084	Yes
Sex.....	No correlation		No correlation		No correlation	
Nutrition.....	No correlation		No correlation		No correlation	
Average mucosal thickness (over 10 years).....	1.06 ± 0.147 mm.		0.98 ± 0.256 mm.		1.03 ± 0.189 mm.	

amount of infiltrate and metaplasia present in this group. There is a similar negative but not statistically significant correlation between mucosal thickness and age in all groups. The negative correlation coefficient between mucosal thickness and the number of lymphoid aggregates is so near 0 as to be entirely insignificant. Therefore, it is obvious that there is a definite and provable tendency for thin mucosas to be associated with heavy leukocytic infiltrate and large amounts of intestinal metaplasia. A tendency is also suggested, but only suggested, for these thinner mucosas to occur in the older age groups. Differences in sex and variations in nutritional state would appear to have no effect on the mucosal thickness.

There is a significant and positive correlation between the number of lymphoid aggregates and increasing age in groups B and C, but this is erased by the presence of cancer in the stomachs in group D. There is a high correlation between the number of lymphoid aggregates and the amount of leukocytic infiltrate in all groups. The positive correlation between nutritional state and the number of lymphoid aggregates only in group C is significant, though there is no apparent explanation for it. The positive correlation between variation in lymphoid aggregates and

intestinal metaplasia in groups C (from persons with extragastric carcinoma) and D (from persons with cancer of the stomach) is also unaccountably less marked and statistically not significant in group A (from "normal" persons). It is clear, then, that with an increase in the number of lymphoid aggregates there is a strong tendency toward a proportionate increase in the amount of leukocytic infiltrate, and that usually this increase is associated with intestinal metaplasia. There is also a tendency for these increases in lymphoid aggregates to be found in the specimens from the older age groups, providing cancer of the stomach is absent. Differences in sex and variations in mucosal thickness show no correlation with changes in lymphoid tissue.

The correlation of the amount of leukocytic infiltrate with other variables is the most striking and clearcut among those analyzed. There is a very high positive

TABLE 6.—*Correlation of Number of Lymphoid Aggregates with Other Mucosal Factors*

	Group B		Group C		Group D	
	Correlation Coefficient	Significance	Correlation Coefficient	Significance	Correlation Coefficient	Significance
Age (by decades).....	$+0.335 \pm 0.079$	Yes	$+0.251 \pm 0.077$	Yes	$+0.023 \pm 0.079$	No
".....	$+0.036 \pm 0.093$	No	$-0.235 \pm 0.073$	Yes	No correlation	No
".....	$-0.062 \pm 0.081$	No	$-0.070 \pm 0.084$	No	$-0.157 \pm 0.084$	No
".....	$+0.583 \pm 0.079$	Yes	$+0.752 \pm 0.077$	Yes	$+0.443 \pm 0.079$	Yes
Sex.....	$+0.170 \pm 0.079$	No	$-0.513 \pm 0.077$	Yes	$-0.372 \pm 0.079$	Yes
Mean amount lymphoid aggregates.....	15.26 $\pm$ 0.535		9.63 $\pm$ 0.463		21.70 $\pm$ 0.559	

Difference in mean amounts of groups B and C is  $3.63 \pm 0.710$ , significant

TABLE 7.—*Correlation of Amount of Leukocytic Infiltrate with Other Factors*

	Group B		Group C		Group D	
	Correlation Coefficient	Significance	Correlation Coefficient	Significance	Correlation Coefficient	Significance
Age (by decades).....	$+0.471 \pm 0.079$	Yes	$+0.378 \pm 0.077$	Yes	$+0.215 \pm 0.079$	No
Nutritional state.....	$+0.041 \pm 0.093$	No	$+0.305 \pm 0.073$	Yes	No correlation	No
Mucosal thickness.....	$-0.233 \pm 0.081$	Yes	$+0.032 \pm 0.084$	No	$-0.445 \pm 0.084$	Yes
Lymphoid aggregates.....	$+0.583 \pm 0.079$	Yes	$+0.752 \pm 0.077$	Yes	$+0.443 \pm 0.079$	Yes
Intestinal metaplasia.....	$+0.512 \pm 0.079$	Yes	$+0.736 \pm 0.077$	Yes	$+0.662 \pm 0.079$	Yes
Sex.....	No correlation		No correlation		No correlation	
Mean amount of infiltrate.....	9.56 $\pm$ 0.369		7.18 $\pm$ 0.371		14.04 $\pm$ 0.345	

Difference of mean amounts of infiltrate of groups B and C is  $2.38 \pm 0.524$ , significant

correlation between the amount of infiltrate present and the amount of metaplasia and dedifferentiation present in all groups, and an almost equally high positive correlation between the amount of infiltrate and the number of lymphoid aggregates present in all groups. The positive and significant correlation between age and the amount of infiltrate in groups of persons who did not have cancer of the stomach is somewhat obscured by the effect of the cancer on the mucosa in those with gastric carcinoma. The negative significant correlation between the amount of infiltrate and mucosal thickness in persons who died acute deaths and those with cancer of the stomach is apparently completely altered in the instance of those who died slow deaths of extragastric cancer, because of the significantly diminished amount of infiltrate in the latter group. In general, it may be said that variations in leukocytic infiltrate are interrelated with changes in the other characteristics of the stomach. Increasing amounts of leukocytic infiltrate may be expected to be found in stomachs with cancer, in association with increasing amounts of intestinal metaplasia and

glandular dedifferentiation, in association with increased numbers of lymphoid aggregates and with advancing age. Lessened infiltration tends to be associated with emaciation and thinner mucosas. The amount of infiltrate is independent of sex.

Most of the variations associated with changes in amounts of intestinal metaplasia have been mentioned. There remain the definite positive correlations between the amount of intestinal metaplasia and the number of lymphoid aggregates in patients who died of extragastric cancer and those with gastric carcinoma. The correlation is so lessened in the group who died relatively acute deaths as not to be statistically significant. There is also an exactly similar group of correlation coefficients between the amount of metaplasia and mucosal cysts. The amount of metaplasia present in a stomach, therefore, tends to increase with age and is much greater in the presence of cancer of the stomach. Such increases tend to be correlated with increasing amounts of lymphoid aggregates, leukocytic infiltrate, mucosal cysts and thinning of the mucosa. Sex again appears to have no influence on the incidence or on the amount of intestinal metaplasia present.

TABLE 8.—*Correlation of Amount of Intestinal Metaplasia and Pyloric Gland Heterotopia with Other Factors*

	Group B		Group C		Group D	
	Correlation Coefficient	Significance	Correlation Coefficient	Significance	Correlation Coefficient	Significance
Age (by decades).....	$+0.303 \pm 0.079$	Yes	$+0.293 \pm 0.077$	Yes	$+0.312 \pm 0.079$	Yes
Mucosal thickness.....	$-0.493 \pm 0.081$	Yes	$-0.193 \pm 0.084$	No	$-0.439 \pm 0.084$	Yes
Lymphoid aggregates.....	$+0.170 \pm 0.079$	No	$+0.513 \pm 0.077$	Yes	$+0.572 \pm 0.079$	Yes
Leukocytic infiltrate.....	$+0.512 \pm 0.079$	Yes	$+0.736 \pm 0.077$	Yes	$+0.662 \pm 0.079$	Yes
Mucosal cysts.....	$+0.163 \pm 0.079$	No	$+0.416 \pm 0.077$	Yes	$+0.316 \pm 0.079$	Yes
Sex .....	No correlation		No correlation		No correlation	
Nutritional state.....	No correlation		No correlation		No correlation	
Mean amount of metaplasia..	$5.30 \pm 0.414$		$4.30 \pm 0.360$		$14.12 \pm 0.599$	

#### SUMMARY

Intestinal metaplasia, pyloric gland heterotopia, mucosal cysts instances of dedifferentiation of specialized cells and lymphoid collections are not present at birth and must therefore develop postnatally, probably as a result of mucosal damage.

Mucosal development is not complete at birth and is not complete until the beginning of the second decade, at which point it reaches a plateau maintained until the sixth decade, when a slight decline begins.

The glands of Brunner attain their adult appearance about the end of the first year of life.

It is suggested that the cardiac glands of the stomach are of esophageal rather than gastric origin. They become fully developed during the first decade of life.

We are unable to substantiate the theory of "digestive leukocytosis" with our material.

Parietal cells may normally be found extending into the duodenal mucosa.

There is a steady increase in the number of lymph follicles and lymphoid collections in the gastric mucosa until the fourth decade, after which the increase tapers off.

There is a slight but steady increase in the amount of leukocytic infiltrate present with the passage of each decade of life without reference to any special type of cell.

Intestinal metaplasia, heterotopia of the pyloric glands, mucosal cysts, heavy leukocytic infiltration and large numbers of lymphoid aggregates are never found in truly normal stomachs but are all evidences of gastritic changes.

Stomachs of patients who died of cancer other than gastric cancer are essentially identical with those who died from other causes, except that they contain fewer lymphoid follicles and collections, and less leukocytic infiltrate. This difference is directly proportional to the degree of malnutrition present and not due to the presence of cancer itself in the patient.

Eighty-two per cent of stomachs from apparently normal persons who died within the gastric cancer age (over 40) show microscopic evidence of chronic atrophic gastritis.

Sixty-six per cent of stomachs from persons over 40 who died of extragastric cancer show microscopic evidence of chronic atrophic gastritis.

Ninety-seven per cent of stomachs with gastric carcinoma show associated chronic atrophic gastritis.

There is a similar incidence of chronic atrophic gastritis in association with gastric diseases other than carcinoma.

The chronic atrophic gastritis associated with gastric carcinoma is a nonspecific "reaction" to inflammation and gastric injury in general, and there is no evidence to suggest an etiologic relationship other than that chronic atrophic gastritis may be caused or intensified by the presence of carcinoma in the stomach.

The factors included in the present concept of chronic atrophic gastritis, i. e. mucosal atrophy, increased amounts of leukocytic infiltrate and lymphoid aggregates, intestinal metaplasia and pyloric gland heterotopia are all rather closely correlated, variation in one factor tending to be associated with proportionate changes in the others. This correlation probably justifies the consideration of these changes as a pathologic entity.

#### CONCLUSION

The often reiterated claim that chronic atrophic gastritis is a precancerous lesion receives no positive support as a result of this study. The slight difference in incidence of gastric atrophy between cancerous and noncancerous stomachs in this series is far from being convincing. Atrophic gastritis is an exceedingly common condition with advancing age. Mere statistical correlation of incidence of gastric atrophy and of gastric cancer is quite insufficient to show causal relation. Both atrophy and cancer appear to be events in aging organs. Were the effort made, it would doubtless be easy to show that gastric cancer was correlated not only with gastric atrophy but likewise with atrophy of other organs, even in fact with atrophy of such anatomically unrelated structures as the genitalia, breasts, circulatory apparatus or even skin, thus reducing to absurdity the conclusions based on mere statistics as to incidence.

To assert on morphologic grounds that the origin of gastric cancer depends on the existence of gastric atrophy would require far more evidence. It would at least require proof that early gastric cancer begins in, and can be directly traced to, an area of atrophy to the exclusion of other areas. From the very nature of gastric material universally available in large clinics, this type of evidence, although it may eventually appear, will be long in coming. Could even this be proved correct, the larger question would still remain unanswered as to why A, with gastric atrophy, gets cancer and B, with the same atrophy, does not. Prematurity in formulating important conclusions in matters of this sort is unjustified.

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# METABOLIC ABNORMALITIES IN PATIENTS WITH CANCER OF THE GASTROINTESTINAL TRACT

A REVIEW OF RECENT STUDIES

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Because of the high incidence and mortality of gastrointestinal cancer<sup>1</sup> its study has been given considerable attention in the Memorial Hospital for the Treatment of Cancer and Allied Diseases. A program has been designed for the investigation of the associated metabolic abnormalities. A detailed study of this nature is believed to be important for two reasons: (1) Through it some clue may be found as to the cause of the disease, and (2) information may be secured by means of which the morbidity and mortality resulting from operative and radiologic procedures can be reduced.

The results of numerous clinical and experimental studies suggest that dietary factors are important in the maintenance of a normal gastrointestinal mucous membrane.<sup>2</sup> Hence a study of the nutritional status of patients with intestinal neoplasms might demonstrate inability to metabolize properly various dietary constituents. Thus far the subjects of the detailed studies which have been made on patients with gastrointestinal cancer are: (A) disturbances in distribution of vitamin A, (B) the incidence, nature and cause of the associated hypoproteinemia, (C) hepatic dysfunction, and (D) the metabolic abnormalities which complicate the postoperative period.

## A. DISTURBANCES IN DISTRIBUTION OF VITAMIN A

Plasma levels of vitamin A and of carotene were determined for 62 normal men and for 62 normal women (table 1) by methods described in an earlier communication of this series.<sup>3</sup> These control subjects varied in age from 20 to 68

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This review of certain aspects of the metabolic abnormalities associated with gastrointestinal cancer is the eighteenth article of this series.

1. Collins, S. D.; Gover, M., and Dorn, H.: Trend and Geographic Variation in Cancer Mortality and Prevalence, with Special Reference to Gastric Cancer, *J. Nat. Cancer Inst.* **1**:425, 1941.

2. (a) Rhoads, C. P.: Gastric Cancer as a Sequel to Gastritis, Particularly the Gastritis of Pernicious Anemia, *J. Nat. Cancer Inst.* **1**:511, 1941. (b) Klein, A. J., and Palmer, W. L.: Experimental Gastric Carcinoma: A Critical Review with Comments on the Criteria of Induced Malignancy, *ibid.* **1**:559, 1941.

3. Abels, J. C.; Gorham, A. T.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract: I. Plasma Vitamin A Levels in Patients with Malignant Neoplastic Disease, Particularly of the Gastro-Intestinal Tract, *J. Clin. Investigation* **20**:749, 1941.

years; all apparently were in good health and on adequate diets. The average plasma vitamin A content of the 62 men was found to be 170.3 U. S. P. units per hundred cubic centimeters with a range of from 132 to 208 U. S. P. units. The average carotene content of this group was 0.21 mg. per hundred cubic centimeters, and the range was from 0.09 to 0.34 mg. A similar study of the 62 normal women gave an average plasma vitamin A content of 149.1 U. S. P. units per hundred cubic centimeters and a range of from 103 to 195 U. S. P. units. The average carotene content was 0.18 mg. per hundred cubic centimeters, and the range was from 0.08 to 0.40 mg.

In distinct contrast to these findings were the levels of vitamin A in the plasma of patients with gastrointestinal cancer (table 1). In 38 men the plasma levels of the vitamin ranged from 32 to 180 U. S. P. units per hundred cubic centimeters and averaged 84 U. S. P. units, or about one-half the normal value. The average carotene of this group content was 0.14 mg. and ranged from 0.04 to 0.50 mg. A study of 13 female patients with cancer of the gastrointestinal tract provided similar data. The plasma vitamin A levels ranged from 50 to 148 U. S. P. units and averaged 78.5 U. S. P. units per hundred cubic centimeters, again about one-half the normal value. The average amount of carotene in the plasma of this group was 0.135 mg. per hundred cubic centimeters, and the levels ranged from 0.05 to

TABLE 1.—*The Plasma Levels of Vitamin A and Carotene in Normal Persons and in Patients with Gastrointestinal Cancer*

	Vitamin A, U. S. P. Units per 100 Cc.		Carotene, Mg. per 100 Cc.	
	Range	Average	Range	Average
62 normal men.....	132-208	170.3	0.09-0.34	0.21
38 men with gastrointestinal cancer.....	32-180	84.0	0.04-0.50	0.14
62 normal women.....	103-195	149.1	0.08-0.40	0.18
13 women with gastrointestinal cancer.....	50-148	78.5	0.05-0.27	0.135

0.27 mg. Of the 51 patients, 86 per cent had vitamin A levels below the normal range, and 96 per cent had levels lower than the average.

The explanation for the discovery that patients with gastrointestinal cancer have low plasma levels of vitamin A was considered at first to be an insufficient intake of carotenoids, due possibly to a deficiency of carotenoids in the diet or to malabsorption of carotenoids from the gastrointestinal tract. However, a deficient intake of carotenoids could not explain the low plasma vitamin A levels in the patients studied, for the following reasons:

1. According to their dietary histories 75 per cent of the patients had ingested normal amounts of carotenoids.
2. Only 15 per cent of a control group of 20 patients with oral leukoplakia and none of a control group of 13 patients with atrophic gastritis had reduced levels of plasma vitamin A. These persons had dietary and economic backgrounds similar to those of the patients with cancer.
3. Fifty-five per cent of the 51 patients with gastrointestinal cancer had normal plasma levels of carotene, the precursor of vitamin A.
4. If the dietary intake of the patients had been inadequate, it might well have been reflected in a deficiency of other dietary constituents. Hence, of 28 patients who had low plasma levels of vitamin A and normal plasma levels of carotene, 13 were examined further for deficiency of thiamine or riboflavin. None of the 18 was deficient in thiamine, and only 1 was deficient in riboflavin.

5. Most important, perhaps, was the observation that the parenteral administration of from 100,000 to 2,000,000 U. S. P. units of vitamin A was without effect in raising the plasma level of the vitamin in 6 of 8 patients with gastrointestinal cancer, but was effective in all of 8 patients with vitamin A deficiency who were used as controls.

Also, it is unlikely that malabsorption of fat-soluble vitamins could have been responsible for the low levels of vitamin A in the plasma of patients with gastrointestinal cancer. Of the 51 patients studied, only 6 had diarrhea or suffered from persistent vomiting. It is true that in those 6 patients the diarrhea or vomiting might have prevented adequate absorption of vitamin A from the alimentary tract. If this were the reason for the low vitamin A concentration in the plasma of those 6 persons, then low concentrations of the vitamin should have existed in the plasma of patients with benign gastrointestinal lesions who had a comparable degree of diarrhea or vomiting. However, of 8 patients with peptic ulcers who had considerable vomiting and of 6 patients with colitis who had persistent diarrhea, only 2 had plasma vitamin A levels below the normal range.

It was evident, then, that patients with gastrointestinal cancer could have low levels of vitamin A in the plasma despite adequate ingestion and absorption of the vitamin. The explanation next considered was that the patients studied suffered from some specific disorder which prevented the normal storage or distribution of the vitamin. Under normal circumstances, it is the function of the liver to store and to distribute vitamin A.<sup>4</sup> It has been demonstrated repeatedly that the hepatic stores of this vitamin in patients with acute or chronic atrophy of the liver are considerably reduced.<sup>5</sup> It became necessary, therefore, to measure the concentration of vitamin A in specimens of liver procured from the patients with gastrointestinal cancer who were subjected to laparotomy. These measurements were made by a technic described in an earlier communication.<sup>6</sup>

No significant difference was found between the content of vitamin A in the livers of 14 patients with gastrointestinal cancer and that in the livers of 21 persons who died suddenly as a result of accident or of coronary thrombosis. The livers of the subjects used as controls were obtained within three hours after death. For the patients with cancer of the gastrointestinal tract the hepatic concentration of vitamin A ranged from 99 to 2,236 and averaged 697 U. S. P. units per gram of wet tissue. For the 21 control subjects the hepatic content of the vitamin ranged from 186 to 1,302 and averaged 722 U. S. P. units per gram of wet tissue. In only 2 of the 14 patients was the hepatic concentration of vitamin A below the normal range. On the other hand, the level of vitamin A in the plasma of 11 of the 14 patients was determined and was found to be abnormally low in all but 1 instance. Eight of the 11 had abnormally low plasma levels of the vitamin associated apparently with a normal ability to store it (table 2).

The administration of vitamin A in amounts adequate to raise the low level in the plasma of patients not having gastrointestinal cancer had only an irregular effect on the plasma levels in patients with the disease.<sup>3</sup> However, other substances were found which could influence appreciably the abnormally low level of vitamin A in the plasma of patients with cancer of the gastrointestinal tract. These

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5. Ralli, E. P.; Papper, E.; Paley, K., and Bauman, E.: Vitamin A and Carotene Content of Human Liver in Normal and in Diseased Subjects: An Analysis of One Hundred and Sixteen Livers, *Arch. Int. Med.* **68**:102 (July) 1941.

6. Abels, J. C.; Gorham, A. T.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Gastrointestinal Cancer: III. The Hepatic Concentrations of Vitamin A, *Proc. Soc. Exper. Biol. & Med.* **48**:488, 1941.

substances were brewers' yeast, lipocaic and choline chloride—themselves free of carotenoids.

All of 17 patients with gastrointestinal cancer who received 90 Gm. of yeast daily for from four to thirty-two days showed a sustained elevation of the plasma level of vitamin A. Likewise the daily administration of 5 Gm. of lipocaic to 7 patients with gastrointestinal cancer for from four to eighteen days was followed in 6 instances by significant, sustained elevations of the plasma levels of the vitamin. Since the possibility exists that both yeast and lipocaic are effective because they contain substances with lipotropic activity, a simple compound with known lipotropic properties, choline chloride, was used. It was administered to 7 patients with gastrointestinal cancer, and during the daily ingestion of 1.5 Gm. for three days, significant but transitory rises in the fasting plasma levels of the vitamin were noted.

The mechanism by which these agents increase the concentration of vitamin A in the peripheral blood is thus far unknown. The possibility of course exists that the lipotropic properties of the yeast, lipocaic and choline, which demobilize lipids from the liver, may be responsible for the increased plasma content of fat-

TABLE 2.—*Concentration of Vitamin A in the Liver and the Plasma of Patients with Gastrointestinal Cancer*

Patient	Sex	Diet	Vitamin A, U. S. P. Units		Microscopic Examination of Liver
			Per Gm. of Liver	Per 100 Cc. of Plasma	
H. G. ....	M	Adequate	1,347	95	Normal
G. H. ....	M	Adequate	1,072	105	Acute focal necrosis
L. G. ....	M	Deficient	756	...	Normal
D. S. ....	M	Adequate	1,017	105	Normal
A. E. ....	M	Adequate	2,236	...	Normal
T. F. ....	M	Adequate	713	120	Normal
J. Y. ....	M	Adequate	196	135	Normal
L. S. ....	M	Adequate	1,226	75	Normal
J. R. ....	M	Deficient	52	40	Normal
E. W. ....	M	Adequate	242	85	Normal
F. R. ....	F	Adequate	195	7	Normal
F. L. ....	F	Adequate	337	90	Normal
E. P. ....	F	Adequate	159	95	Normal
T. B. ....	F	Deficient	948	..	Normal
Average			697 U. S. P. units per Gm.		

soluble vitamin A. This theory is based on the assumption that the lipids in the fatty liver may withhold from the blood the fat-soluble vitamins. Chemical analysis, made in the laboratories of the Memorial Hospital, of the hepatic tissue of patients with gastrointestinal cancer in fact does reveal a high incidence of hepatic fatty infiltration.<sup>7</sup> Of 18 patients thus studied, 16 (or 88 per cent) were found to have a hepatic fat concentration above the reported normal range (2.4 to 8.5 Gm. per hundred grams).<sup>8</sup>

On the other hand, it is quite possible that the abnormal distribution of vitamin A between the liver and the plasma of patients with gastrointestinal cancer is not due simply to the increased fat content of the liver and consequently to its greater

7. (a) Ariel, I.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract: VII. The Influence of Gastric Surgery on the Chemical Composition of the Liver, *Ann. Surg.* **116**:924, 1942. (b) Ariel, I.; Abels, J. C.; Murphy, H. T.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastro-intestinal Tract: VIII. The Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer, to be published. (c) Abels, J. C.; Ariel, I. M.; Murphy, H. T.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: IX. Effects of Dietary Constituents upon the Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer, to be published.

8. Ralli, E. P.; Rubin, S. H., and Rinzler, S.: The Liver Lipids in Normal Human Livers and in Cases of Cirrhosis and Fatty Infiltration of the Liver, *J. Clin. Investigation* **20**:93, 1941.

"hold" on fat-soluble substances. The fact that the excessively fatty livers of well nourished patients who suffer from chronic alcoholism frequently contain very small amounts of vitamin A argues against the hypothesis that the low plasma levels of the vitamin in patients with gastrointestinal cancer are due to the fatty livers.<sup>5</sup> Abnormal plasma levels of the vitamin, therefore, might be due rather to a hepatic dysfunction which prevents the normal distribution of vitamin A between the liver and the plasma.<sup>9</sup>

In summary, then, it has been found that the level of vitamin A in the plasma was below the normal range in 86 per cent of the patients with gastrointestinal cancer examined. In most instances this abnormality could not be explained by the existence of a dietary deficiency, by a malabsorption of the vitamin or by an inability of the liver of the patient to store vitamin A. The administration of yeast, lipocain or choline was effective in raising the reduced plasma levels of vitamin A in these patients. The effect of these substances conceivably was due to their ability to demobilize lipids from the liver. A large number of patients with gastrointestinal cancer do have fatty infiltration of the liver, and the increased fat content in turn may result in a retention of the fat-soluble vitamin A and consequently in a low level of the substance in the plasma. On the other hand, it is possible that a specific hepatic dysfunction in the metabolism of vitamin A prevents a normal distribution of the vitamin.

#### B. THE INCIDENCE, NATURE AND CAUSE OF THE HYPOPROTEINEMIA ASSOCIATED WITH GASTROINTESTINAL CANCER

Hypoproteinemia frequently results in serious clinical complications. Interference with the healing of wounds, actual wound disruption, edema, altered gastrointestinal motility, gastrointestinal obstruction, increased susceptibility to the toxic effects of anesthetics and susceptibility to infection often can be attributed directly to an abnormally low protein level in the patient's serum.<sup>10</sup> Hypoproteinemia when present in patients with gastrointestinal cancer accordingly becomes an especially important problem, because such patients frequently are subjected to prolonged anesthesia and to extensive surgical procedures. For this reason it became essential to ascertain the level of circulating serum proteins in the patients admitted to the gastric and rectal services of this hospital.

Recent studies<sup>11</sup> have indicated that in 547 normal adults the mean average serum protein level was 6.9 Gm. per hundred cubic centimeters, with a normal range of from 6.5 to 7.4 Gm. These values are in substantial agreement with those found in the Memorial Hospital for 25 normal men and women, whose serum protein concentrations ranged from 6.6 to 7.8 Gm. per hundred cubic centimeters.<sup>12</sup>

In sharp contrast to these levels were those in the serum of 100 patients with gastric cancer.<sup>13</sup> The average serum protein concentration of these patients was only 6.2 Gm. per hundred cubic centimeters, and the values varied from 3.9 to 8.0

9. Moore, T.: Vitamin A and Carotene: VII. The Distribution of Vitamin A and Carotene in the Body of the Rat, *Biochem. J.* **25**:275, 1931.

10. Whipple, G. H.: Hemoglobin and Plasma Proteins: Their Production, Utilization and Interrelation, *Am. J. M. Sc.* **203**:477, 1942.

11. Hill, R. H., and Trevorrow, V.: Plasma Albumin, Globulin and Fibrinogen in Healthy Individuals from Birth to Adult Life, *J. Lab. & Clin. Med.* **26**:1838, 1941.

12. Abels, J. C.; Rekers, P. E.; Binkley, G. E.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: II. Hepatic Dysfunction, *Ann. Int. Med.* **16**:221, 1942.

13. Ariel, I.; Rekers, P., and Pack, G. T.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: X. Abnormalities in Protein Metabolism in Patients with Gastric Cancer, to be published.

Gm. Of the 100 patients examined, 59 were found to have abnormally low levels. Thus, hypoproteinemia is an abnormality commonly associated with gastric cancer.

The cause of the hypoproteinemia is still not entirely clear. The most obvious explanations were considered at first to be that (1) the patients with gastric cancer had taken deficient diets, (2) they suffered from continual or repeated bleeding, (3) there existed some metabolic abnormality which prevented the synthesis of serum proteins, (4) the patients could not absorb properly from their gastrointestinal tracts the amino acids necessary for protein synthesis or (5) they destroyed abnormally great amounts of protein.

The possible role of an inadequate dietary intake in the production of hypoproteinemia was investigated for 93 of the 100 patients with gastric cancer. These patients were divided into three nutritional groups, in which there existed: (a) a minimal degree of dietary deficiency, (b) a moderate degree of dietary deficiency and (c) a considerable degree of dietary deficiency. This division revealed that of the 93 patients 42 had only a minimal degree of dietary deficiency, yet 26 of the 42 had hypoproteinemia. Moreover, of the 35 patients whose diets were moderately deficient, only 19 were hypoproteinemic, and of the 16 who suffered from a considerable degree of dietary deficiency, only 8 had abnormally low levels of serum protein. Furthermore, at the low nutritional levels the duration of a deficient dietary intake was considerably less for the subjects in whom hypo-

TABLE 3.—*Degree and Duration of Dietary Deficiency in Patients with Gastric Cancer*

Degree of Dietary Deficiency	Number of Patients with Normal Serum Protein Levels	Average Duration of Deficiency, Weeks	Number of Patients with Hypoproteinemia	Average Duration of Deficiency, Weeks
Minimal.....	16	44.5	26	22.8
Moderate.....	16	16.3	19	11.4
Considerable.....	8	12.1	8	7.2

proteinemia developed than it was for those who retained a normal concentration of serum protein. Thus it would appear that there is no correlation between the existence of hypoproteinemia in the patients with gastric cancer and the duration and degree of dietary deficiency (table 3).<sup>13</sup>

There is now considerable evidence to show that repeated bleeding can result not only in anemia but also in hypoproteinemia.<sup>14</sup> Since patients with gastric cancer frequently suffer from repeated or continual loss of blood, it was necessary to consider this factor among the causes for hypoproteinemia. Accordingly, the 100 patients with gastric cancer were divided into two groups: 42 who at some time had manifested bleeding, and 58 in whose cases no history or other evidence of blood loss could be established. No significant difference, however, could be found between the serum protein levels of these two groups. The mean average protein concentration in the serum of patients who lost blood was 6.1 Gm. per hundred cubic centimeters, whereas that of those who did not was 6.2 Gm. per hundred cubic centimeters.<sup>13</sup>

Certain pathologic processes frequently can induce a hypoproteinemia characterized by a depression of one or another of the serum protein fractions. For this reason it was believed that determination of the albumin and globulin concentration in the serum of patients with gastric cancer might provide some clue as to the nature of their hypoproteinemic state.

14. Whipple, G. H.: The Production, Utilization and Interrelation of Blood Proteins—Hemoglobin and Plasma Proteins, *Proc. Inst. Med. Chicago* 14:2, 1942.

The normal value of serum albumin, determined for a group of 547 normal adults, recently has been reported to be  $4.7 \pm 0.3$  Gm. per hundred cubic centimeters.<sup>11</sup> This value agrees well with that observed here for a control group of 25 persons ( $4.6 \pm 0.7$ ). Likewise, the average concentration of globulin in the serum of the controls has been found here to be  $2.1 \pm 0.6$  Gm. per hundred cubic centimeters, a figure which is in close agreement with that reported by other workers.<sup>11</sup>

By these standards it was found that the hypoproteinemia in 77 per cent of the patients with gastric cancer was principally due to a decreased albumin fraction (table 4). For 28 patients thus studied, the mean average serum albumin was found to be  $3.8 \pm 0.62$  Gm. per hundred cubic centimeters. All had concentrations of serum albumin below the normal average of 4.6 Gm. per hundred cubic centimeters, and 65 per cent had concentrations below the normal range (table 4).

No significant differences were noted between the concentration of globulin in the serum of the patients with gastric cancer and that in the serum of persons used as controls. Hence it would appear that in patients with gastric cancer, there exists an abnormality in the maintenance and replacement of serum albumin. It is this defect, apparently, which accounts in most instances for the hypoproteinemia.<sup>13</sup>

In turn, the inability of the patient with gastric cancer to fabricate albumin may be due either to an abnormality of protein metabolism in which the liver plays

TABLE 4.—Concentrations of Serum Protein, Albumin and Globulin in Patients with Gastric Cancer

Subjects	Total Protein, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.
Control group .....	$6.7 \pm 0.6$	$4.6 \pm 0.7$	$2.1 \pm 0.6$
Reported by Hill and Trevorrow <sup>11</sup> for normal adults	$6.9 \pm 0.4$	$4.7 \pm 0.3$	$2.0 \pm 0.3$
Patients with gastric cancer.....	$3.8 \pm 0.7$	$3.3 \pm 0.6$	$2.2 \pm 0.4$

an important role or to an insufficient supply of nitrogenous compounds. To date the best available evidence indicates that albumins are synthesized chiefly by the liver.<sup>15</sup> The liver of a person who is hypoproteinemic on the basis of dietary deficiency readily can fabricate albumin from a proper mixture of amino acids, but the synthesis of protein from amino acids in the damaged liver may be altered considerably.<sup>16</sup>

The data presented already have indicated that the hypoproteinemia of the patients with gastric cancer probably was not due to a general dietary restriction. However, there was still the possibility that in these patients the absorption of amino acids might be impaired. This was substantiated.<sup>17</sup> The ingestion of 25 Gm. of aminoacetic acid by a group of 6 control subjects in whom there was no evidence of gastrointestinal disease was followed by a maximum absorption of the compound within the first hour. In contrast, it was observed after the administration of 25 Gm. of aminoacetic acid to 6 patients with gastrointestinal cancer that the peak

15. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization, *Physiol. Rev.* 20:194, 1940.

16. Cates, H. B.: The Relation of Liver Function to Cirrhosis of the Liver and to Alcoholism: Comparison of Results of Liver Function Tests with Degree of Organic Change in Cirrhosis of Liver and with Results of Such Tests in Persons with Alcoholism Without Cirrhosis of Liver, *Arch. Int. Med.* 67:383 (Feb.) 1941.

17. Ariel, I.; Jones, F.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract: XII. Glycine Tolerance Test in Patients with Gastric Cancer, *Ann. Surg.* 117:740 (May) 1943.

of absorption was considerably delayed in all. This delayed absorption of amino acids apparently does not depend merely on the presence of organic gastrointestinal disease, for a normal rate of absorption of aminoacetic acid was noted in 1 patient with atrophic gastritis, 1 with multiple gastric ulcers and 1 with gastric Boeck's sarcoid. Furthermore, normal absorption of this amino acid was noted in 3 patients who had undergone gastrectomy.

It would appear, therefore, that one cause for the impaired production of protein by patients with gastric cancer may be an inability to absorb amino acids properly from the alimentary tract. Furthermore, it is possible that the liver, perhaps because of hepatic dysfunction, cannot fabricate proteins at a proper rate or in sufficient amounts from the amino acids which have been absorbed. This hypothesis is supported by experimental observations.<sup>17</sup> Whereas the ingestion of 25 Gm. of aminoacetic acid increased the average concentration of amino acids in the serum of normal persons by 2.9 mg. per hundred cubic centimeters (range of increase from 1.9 to 5.9 mg. per hundred cubic centimeters), the average increase in the serum of 6 patients with gastric cancer was 0.6 mg. (range of increase from 4.1 to 8.8 mg.). A high level of amino acids in the serum of a person given aminoacetic acid orally has been demonstrated to indicate inability of the liver to utilize that compound at a normal rate.<sup>18</sup>

The possibility is still to be investigated that the hypoproteinemia of the patient with gastric cancer may be due in part to an increased breakdown of protein. The total excretion of nitrogen of 10 patients with gastric cancer has been measured. When these patients were taking constant, known amounts of dietary protein, their daily excretion of nitrogen was no greater than that of normal persons on the same diet. These observations indicate that patients with gastric cancer do not have an abnormally great loss of nitrogen. Studies of this nature now are being extended.

In conclusion, therefore, it was found that 59 per cent of patients with gastric cancer suffer from hypoproteinemia. This abnormality probably cannot be ascribed to the fact that the patients studied suffered from a general dietary deficiency or from excess bleeding, but it more likely is due to a metabolic abnormality which interferes with the maintenance and replacement of serum albumin.

Since the serum albumins are fabricated chiefly by the liver, these observations suggest that the hypoalbuminemia conceivably is due to hepatic dysfunction. The impaired absorption of amino acids from the alimentary tract of patients with gastric cancer probably contributes to the establishment of the hypoproteinemic state.

### C. HEPATIC DYSFUNCTION IN PATIENTS WITH GASTROINTESTINAL CANCER

The evidence derived from the studies thus far described suggests that patients with gastrointestinal cancer suffer from hepatic insufficiency. This evidence consists chiefly of data showing that the patients apparently had a limited ability to distribute vitamin A or to fabricate albumin—both known functions of a normal liver. Hence, it became desirable to investigate in greater detail other hepatic functions of patients with cancer of the gastrointestinal tract and to correlate, if possible, the existence of hepatic dysfunction with the presence of the cancer.

Accordingly, an estimation of hepatic function in each of 50 patients with gastrointestinal cancer was obtained from the results of tests which measured the

18. Kirk, E.: The Ability of Nephritic Patients to Deaminate and Form Urea from Ingested Glycine, *J. Clin. Investigation* 14:136, 1935.



ability of the liver to synthesize, store, conjugate and excrete metabolites. A similar study was made for purposes of comparison on 25 normal adults, on 21 patients with oral leukoplakia, on 8 with atrophic gastritis and on 19 who had had a gastrointestinal cancer successfully removed by operation.<sup>12</sup>

Inasmuch as the liver performs multiple functions, it is reasonable to believe that no single test can measure adequately the efficiency of the whole organ. After the measurement qualitatively, and when possible quantitatively, of various intermediary or end products of hepatic metabolism, a consideration of all the results may allow the detection of abnormal hepatic function.

In this study measurements of hepatic function were selected arbitrarily. The basis of their usefulness and reliability was presented in a previous communication.<sup>12</sup> Suffice it to say that hepatic abnormality was considered to be present in the persons examined when (1) the plasma prothrombin level was less than 85 per cent of normal, (2) the serum bilirubin was above 1 mg. per hundred cubic centimeters, (3) the urinary excretion of glucuronates was less than 300 mg. per day, (4) the mean erythrocyte volume was greater than 94 cubic microns, (5) the free cholesterol was more than 33 per cent of the total, (6) the urinary excretion

TABLE 5.—*Comparison of the Results of Studies of Hepatic Function on Normal Persons and on Groups of Patients Studied*

	Normals	Leukoplakia of the Oral Mucous Membranes	Atrophic Gastritis	Cancer of the Gastro- intestinal Tract	Cancer of the Gastro- intestinal Tract Removed
Number of patients.....	25	21	8	50	19
Hepatomegaly.....	0%	20%	37.5%	42%	16%
Elevated serum bilirubin.....	4%	10%	12.5%	24%	5%
Decreased serum protein.....	0%	0%	0%	55%	5%
Decreased plasma prothrombin.....	4%	25%	0%	55%	33%
Impaired cholesterol esterification....	12%	6%	12.5%	45%	19%
Increased mean corpuscular volume of erythrocytes.....	8%	20%	0%	60%	23%
Decreased plasma vitamin A.....	4%	19%	0%	90%	34%
Decreased urinary excretion of glucu- ronates.....	8%	24%	12.5%	55%	14%

of urobilinogen was more than 2.0 mg. per day when the fecal output of the pigment was normal and (7) hepatomegaly was demonstrable.

By these criteria it was found that of the 25 normal adults 19 (76 per cent) had no hepatic abnormalities, 4 (16 per cent) had one such abnormality and only 2 (8 per cent) had as many as two signs of hepatic insufficiency. In sharp contrast to these results were those of a similar study of the 50 patients with gastrointestinal cancer. Only 1 of this group was free of evidence of hepatic insufficiency; 7 (14 per cent) had one, 13 (26 per cent) had two, 13 (26 per cent) had three, 11 (22 per cent) had four, 3 (6 per cent) had five, and 2 (4 per cent) had six or more signs of hepatic dysfunction.

Measurements were likewise made of the hepatic function of 2 other groups of patients, 1 with atrophic gastritis and the other with oral leukoplakia, because these patients probably resembled the patients with gastrointestinal cancer more closely in age, dietary and economic background than did the normal subjects. In both control groups the degree and extent of hepatic insufficiency were only slightly greater than in the normal persons, and considerably less than in patients with cancer of the alimentary tract (table 5).

The occurrence of a considerable degree of hepatic dysfunction in patients with gastrointestinal cancer, therefore, would support the hypothesis that the abnormal

levels of vitamin A and the hypoproteinemia likewise were the result of altered hepatic function. It is of considerable interest to note that despite the high incidence of hepatic insufficiency manifested by patients with gastrointestinal cancer the liver shows little or no morphologic change. Of biopsy specimens obtained from the livers of 55 patients with gastric cancer, 49 showed no pathologic changes; of the remaining 6 specimens, 1 showed hepatitis, 2 fatty infiltration, 2 acute focal necrosis and 1 a mild fibrosis. In none of the 55 specimens was there enough parenchymal destruction to suggest the considerable hepatic insufficiency noted in patients with gastrointestinal cancer.<sup>7</sup>

Although little or no morphologic evidence of damage was found in the biopsy specimens obtained from the livers of patients with cancer of the gastrointestinal tract, nevertheless it is possible that the chemical composition of these livers was abnormal. It is now well proved that livers with a high content of fat<sup>19</sup> or a depleted store of glycogen<sup>20</sup> are particularly susceptible to damage by such agents as chloroform, phosphorus, arsenic and carbon tetrachloride. The association of hepatic dysfunction with an altered chemical composition of the liver already has been demonstrated in persons with chronic alcoholism.<sup>21</sup>

Accordingly chemical analyses were made of biopsy specimens removed from the livers of 18 fasting patients with gastric cancer. These specimens were obtained as soon as the abdomen was opened.<sup>17</sup> An adequate comparison of the findings with normal values is, of course, impossible at this time because of a paucity of data on normal persons.

The normal value of human hepatic glycogen probably is not known. The hepatic glycogen content of persons who received preoperatively large amounts of dextrose has been stated to range from 3.1 to 6.7 Gm. per hundred grams.<sup>22</sup> The hepatic glycogen of 4 patients with non-neoplastic gastrointestinal disorders, determined in our laboratories, averaged 2.28 Gm. per hundred grams and varied from 1.30 to 3.55 Gm. (table 6). A slightly higher average value was obtained for the glycogen content in the livers of the 18 patients with gastric cancer, 2.91 Gm. per hundred grams, and the range for these livers was from 1.0 to 7.3 Gm. However, under the stress of the operation the content of hepatic glycogen is decreased considerably.<sup>2a</sup> In 10 instances in which the glycogen was determined in sections removed for biopsy at the beginning and at the end of an operation, all showed a significant decrease in the content of the carbohydrate. The average loss of glycogen of these 10 patients was 1.96 Gm. per hundred grams, and the range of loss was from 0.75 to 3.81 Gm. This decrease represented an average of 37 per cent of the glycogen present at the beginning of the operation.

By the preoperative administration of dextrose, it was possible to increase the hepatic glycogen content of 11 patients with gastric cancer to an average concentration of 4.39 Gm. per hundred grams, a concentration considerably less than

19. Goldschmidt, S.; Vars, H. M., and Ravdin, I. S.: The Influence of Foodstuffs upon the Susceptibility of the Liver to Injury by Chloroform and the Probable Mechanism of Their Actions, *J. Clin. Investigation* **18**:277, 1939.

20. Messinger, W. J., and Hawkins, W. B.: Arsphenamine Liver Injury Modified by Diet: Protein and Carbohydrate Protective, but Fat Injurious, *Am. J. M. Sc.* **199**:216, 1940.

21. Ralli, Rubin and Rinzler,<sup>8</sup> Madden and Whipple.<sup>15</sup>

22. (a) MacIntyre, D. S.; Pedersen, S., and Maddock, W. G.: The Glycogen Content of the Human Liver, *Surgery* **10**:716, 1941. (b) Ravdin, I. S.; Vars, H. M.; Thorogood, E.; Schultz, J., and Johnson, J.: The Liver Glycogen and Lipid Concentrations Following Intravenous Glucose Administration and Diet in the Dog and Man in the Presence of Liver Damage. *Ann. Surg.* **114**:1018, 1941.

that obtained after similar treatment in 6 patients with non-neoplastic gastrointestinal disease (7.35 Gm. per hundred grams), and with that obtained elsewhere.<sup>22b</sup>

Determinations of human hepatic protein, albumin and globulin, were made by an adaptation of the method of Robinson, Price and Hogden.<sup>23</sup> The details of that technic were reported in an earlier communication.<sup>7</sup> It is to be emphasized, however, that by the terms hepatic "albumin" and "globulin" are meant only those fractions which can be separated by precipitation with a 22 per cent solution of sodium sulfate at 37 C. It is not implied that these fractions exist as such in the liver or are identical with the albumin and globulin of the serum.

By this technic the average protein content in the livers of 4 patients with non-neoplastic gastrointestinal disease was found to be 14.6 Gm. and the range from 11.4 to 16.6 Gm. per hundred grams; the "albumin" averaged 3.65 Gm. and ranged

TABLE 6.—*The Chemical Composition of the Human Liver*

Subjects	Glycogen, Gm. per 100 Gm.		Fat, Gm. per 100 Gm.		Protein, Gm. per 100 Gm.		Albumin, Gm. per 100 Gm.		Globulin, Gm. per 100 Gm.	
	Range	Average	Range	Average	Range	Average	Range	Average	Range	Average
4 patients with non-neoplastic gastrointestinal disease	1.33- 3.55	2.28	6.2- 17.0	11.8	11.4- 16.6	14.6	1.0- 4.7	3.65	6.7- 14.05	10.47
6 patients with non-neoplastic gastrointestinal disease after preoperative dextrose (250 Gm.)	5.25- 9.45	7.35	2.3- 8.5	6.19	11.4- 15.8	13.80	1.5- 4.4	3.10	8.9- 12.9	11.11
18 patients with gastrointestinal cancer	1.0- 7.3	2.91	5.3- 35.0	17.47	12.9- 17.95	16.17	3.2- 8.05	5.27	8.0- 14.6	10.59
11 patients with gastrointestinal cancer after preoperative dextrose (250 Gm.)	2.3- 9.95	4.59	3.9- 15.2	7.24	11.9- 17.9	15.32	3.0- 7.1	4.63	8.7- 13.3	10.18
11 patients with gastrointestinal cancer after preoperative lipoene (8 Gm.)	1.1- 4.3	2.67	4.05- 11.1	8.05	14.5- 18.7	16.13				
7 patients with gastrointestinal cancer after preoperative choline chloride (3 Gm.)	1.1- 6.6	3.19	6.9- 16.1	11.21						
8 patients with gastrointestinal cancer after preoperative inositol (1.2 Gm.)	1.5- 4.95	3.28	3.5- 16.7	6.94						

from 1.05 to 4.7 Gm., and the "globulin" averaged 10.24 Gm. and ranged from 6.7 to 14.05 Gm. No significant difference appeared to exist between these values and the corresponding values which were obtained for a group of 18 patients with gastric cancer. The total protein in the livers of these patients ranged from 12.9 to 17.9 Gm. and averaged 16.17 Gm. per hundred grams; the "albumin" ranged from 3.2 to 8.05 Gm. and averaged 5.27 Gm., and the "globulin" ranged from 8.0 to 14.6 Gm. and averaged 10.59 Gm. Moreover, no correlation could be found between the concentration of protein in the liver and that in the serum of the patients studied.<sup>7b</sup>

It is interesting to note that the liver apparently does not contain large stores of "albumin." Assuming an average weight of the liver of 1,500 Gm., the average concentration of 4.1 Gm. per hundred grams obtained for hepatic "albumin" would signify a total of only 61.5 Gm. of protein, or about one fourth of the amount of protein of the normal circulating serum albumin. Thus, if the "albumins" of the

23. Robinson, H. W.; Price, J., and Hogden, C. G.: The Estimation of Albumin and Globulin in Serum: I. A Study of the Errors Involved in the Filtration Procedure, *J. Biol. Chem.* 120:481, 1937.

liver are similar to those of the serum or are converted readily into that fraction, the store they constitute for replacement of serum albumin is a small one.

The lipid content of 100 normal human livers obtained within a few hours after accidental death has been reported to range from 2.42 to 8.50 Gm. and average 4.98 Gm. per hundred grams.<sup>6</sup> By these standards it was found that 15 of 18 patients with gastric cancer had abnormally high values of hepatic lipid (greater than 8.50 Gm. per hundred grams). The average lipid content in the livers of these patients, who were made to fast preoperatively, was 17.27 Gm. and the range from 5.30 to 35.0 Gm. per hundred grams of wet tissue.

However, not only do patients with gastrointestinal cancer have an abnormally high content of hepatic lipid, but the abnormality frequently may be aggravated further by the operative procedures which they undergo.<sup>7a</sup> Of 11 patients from whose livers biopsy specimens were obtained at the beginning and at the conclusion of a three hour operation, 7 had an increase in the fat content of the liver at the end of the operation. The average increase of the hepatic lipid was 1.95 Gm. per hundred grams, and the range of increase was from 1.0 to 3.2 Gm. per hundred grams. These alterations probably represent an influx of fat to livers already so damaged as to be unable to metabolize it. The concentration of fat in the livers of the remaining 4 patients did not rise.

The possibility was considered that since fat is mobilized into the liver during starvation,<sup>7c</sup> the usual twelve to eighteen hour preoperative fast might per se account for the high content of lipid in the livers of the patients with gastric cancer. For that reason, 17 patients, 11 with gastric cancer and 6 with benign gastrointestinal lesions, each was given 250 Gm. of dextrose during the ten hours preceding operation. After this therapy the lipid content in the livers of the 6 patients with benign lesions was within normal limits and averaged 6.19 Gm. per hundred grams; that of the 11 patients with gastric cancer was 7.24 Gm. per hundred grams. These findings, therefore, suggest that the deposits of fat in the livers of patients with gastric cancer may be decreased by the preoperative ingestion of sugar.

The same effect can be accomplished in these patients by the preoperative administration of lipocaic. In 11 patients with gastrointestinal cancer who received 8 Gm. of this material preoperatively, the average fat content of the livers was only 8.05 Gm. per hundred grams. The effect of lipocaic probably was not due to its content of choline, but might be due to its inositol component (table 6).<sup>7c</sup>

That the presence of gastrointestinal cancer, even when it is restricted to its site of origin, plays a significant role in the development of the hepatic insufficiency is shown by the fact that patients who have had a gastrointestinal cancer removed have considerably less evidence of hepatic dysfunction than do those who still bear cancer.<sup>12</sup> Studies of hepatic function now have been made on 19 patients whose gastrointestinal cancer was removed successfully and who had survived free of disease for from two months to ten years after operation. The results indicate that of these 19 patients, 32 per cent had no evidence of hepatic insufficiency, 48 per cent had only one such evidence and 20 per cent had two hepatic abnormalities. Such a difference in the degree and extent of hepatic insufficiency between the patients with gastrointestinal cancer and those who have had such a lesion surgically removed strongly suggests that the very presence of the cancer imposes on the liver a physiologic dysfunction which is in part reversible. Whether or not the removal of the gastrointestinal cancer also is followed by a decreased content of fat and an increased amount of glycogen in the liver is not known. Experiments to secure this information now are under way.

An analogous situation has been noted in animals with hepatomas induced by the carcinogen dimethylaminoazobenzene (butter yellow). The very presence of

the tumor in the organism, even when transplanted to a structure considerably distant from the liver, results in severe hepatic dysfunction, as indicated by a considerable depression in the synthesis of certain enzymes by the liver. The excision of "butter yellow tumors" is followed quickly by a return of normal hepatic function.<sup>24</sup>

The fact that hepatic insufficiency is so closely associated with the presence of gastrointestinal cancer bears repeated emphasis. Patients with cancer of the gastrointestinal tract frequently are subjected to prolonged anesthesia and extensive surgical procedures, which are injurious even to normal livers.<sup>25</sup> It is reasonable to believe that further injury to an already damaged organ might give rise to serious problems during the course of the operation and in postoperative care.<sup>25a</sup>

Even in the normal person, the administration of certain anesthetics and manipulation of the liver have been shown to induce a transitory hepatic insufficiency. The normal liver will recover completely from these effects, but the damaged organ, further impaired by toxic agents, may not return even to its previously reduced functional capacity. Some of the patients herein reported on

TABLE 7.—*The Effect of Loss of Blood on the Size of the Erythrocytes of Patients with Gastrointestinal Cancer*

Patients	Percentage of Patients with		
	Macrocytosis, Mean Corpus- cular Volume Greater than 94 Cubic Microns	Normocytosis, Mean Corpus- cular Volume 80 to 94 Cubic Microns	Microcytosis, Mean Corpus- cular Volume Less than 80 Cubic Microns
20 with loss of blood.....	33	53	10
47 without loss of blood.....	42.5	49	8.5

not only received inhalation anesthetics but were given combinations of large amounts of barbiturates both by mouth and intravenously. These drugs, known to be detoxified by the liver,<sup>26</sup> probably impose an added load on an already damaged organ.

The occurrence of hypoproteinemia, especially when due to impaired hepatic fabrication of protein, is not to be considered a transient phenomenon. Hypoproteinemia in patients with gastrointestinal cancer represents a serious complication which frequently can be treated only by direct replacement of the serum proteins. The high incidence (10 per cent) of wound disruption in a group of 50 patients with gastrointestinal cancer who were hypoproteinemic testifies to the seriousness of the problem at hand.<sup>12</sup>

The high incidence of anemia (73 per cent) in patients with gastrointestinal cancer probably plays an important role in their postoperative course. The anemia in 91 per cent of these patients is either macrocytic or normocytic and usually is refractory to therapy (table 7).<sup>13</sup>

24. Maver, M. E.; Mider, G. B.; Johnson, J. M., and Thompson, J. W.: The Comparative Proteinase and Peptidase Activities of Rat Hepatoma and Normal and Regenerating Rat Liver, *J. Nat. Cancer Inst.* 2:277, 1941.

25. (a) Miller, L. L., and Whipple, G. H.: Chloroform Liver Injury Increases as Protein Stores Decrease: Studies in Nitrogen Metabolism in These Dogs, *Am. J. M. Sc.* 199:204, 1940. (b) Lord, J. W., Jr.; Andrus, W. De W., and Moore, R. A.: Metabolism of Vitamin K and Role of the Liver in Production of Prothrombin in Animals, *Arch. Surg.* 41:585 (Sept.) 1940.

26. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, *Arch. Int. Med.* 61:297 (Feb.) 1938.

Evidently the element of loss of blood influenced but little the type and degree of anemia present in the patients with gastrointestinal cancer, for the incidence of macrocytosis and of microcytosis was as great among patients who had suffered loss of blood as among those who had not (table 7). That anemia can be induced by improper synthesis of hemoglobin from protein already has been demonstrated in patients with acute injury to the liver or with cirrhosis.<sup>10</sup> It is therefore probable that the macrocytic or normocytic anemia found in the patients with gastrointestinal cancer likewise was secondary to hepatic dysfunction and deranged protein metabolism.

A further serious consequence of hepatic dysfunction in patients with gastrointestinal cancer is the factor of hypoprothrombinemia. In contrast to the hypoprothrombinemia due to nutritional deficiency or malabsorption of vitamin K, that which exists in patients with hepatic disease is refractory even to the parenteral administration of large amounts of the vitamin. This observation recently has been confirmed here, too, in 6 patients with cancer of the stomach and in 25 patients with cancer of the large bowel.<sup>27</sup> Furthermore, the severity of the hypoprothrombinemia with few exceptions is increased during and after the operative procedure—often to a point where bleeding tendencies may ensue. At present it would appear that the only means at hand to combat this complication are those directed toward a general improvement of the hepatic dysfunction.

In conclusion, therefore, patients with cancer of the gastrointestinal tract were found to have a high incidence of hepatic dysfunction. This dysfunction may account for the fact that such patients become unable to distribute vitamin A properly and frequently suffer from hypoproteinemia. Although no morphologic changes were noted in the livers of most of the patients, chemical analysis of the tissue often revealed an abnormal content of hepatic lipid.

The existence of hepatic dysfunction in patients with gastrointestinal cancer is especially important because of the augmented hazard it imposes on their operative and postoperative course. Delayed wound healing, refractory anemia and hypoprothrombinemia, impaired fabrication of protein and tendency to infections may all be associated with hepatic insufficiency and possibly may be directly due to it. Moreover, the surgical manipulation and the anesthesia which these patients undergo produce further hepatic insufficiency, deprive the liver of its store of glycogen, and often infiltrate the tissue with fat.

#### D. METABOLIC ABNORMALITIES OF THE POSTOPERATIVE PERIOD

Although many of the metabolic abnormalities found in patients with gastrointestinal cancer subside after the surgical removal of the lesion, these patients nevertheless often have a prolonged and difficult postoperative course. Loss of weight, dyspepsia, hypoprothrombinemia and refractory anemia are especially characteristic of the postoperative period of patients who undergo gastric resection.

1. *Absorption of Fat After Total Gastrectomy.*—In order to ascertain the cause of the postoperative complications, it became necessary to investigate the ability of the patients to digest and absorb from the alimentary tract simple dietary constituents. Thus far, of these dietary constituents, a detailed study has been made only of the absorption of fat by the patients who underwent gastrectomy and by a group of persons used as controls.<sup>28</sup>

27. Abels, J. C.; Binkley, G. E., and Rhoads, C. P.: Unpublished data.

28. Rekers, P. E.; Abels, J. C., and Rhoads, C. P.: Metabolic Abnormalities in Patients with Cancer of the Gastro-Intestinal Tract: IV. Fat Metabolism; a Method of Study, *J. Clin.*

The absorption of fat from the gastrointestinal tracts of the subjects studied was determined by the direct measurement of the fat excreted in the stools. Fifty-four stool specimens of from one to four day periods were collected from 8 control subjects. These persons ate daily basal diets which contained from 35 to 80 Gm. of fat. The lipid content of their stool specimens varied from 1.0 to 6.5 Gm. per day, and the average amount of fat excreted by each individual varied from 2.1 to 5.1 Gm. per day.

In marked contrast to these values were the amounts of fecal lipid excreted by 3 patients who had survived total gastrectomies for from six to eighteen months. Although they had taken a diet which contained only 40 Gm. of fat, their output of fecal fat in all of 13 specimens collected over periods of from three to four days was greater than the largest amount excreted by any one of the control subjects. The amount of fat in the stools of 3 gastrectomized patients was found to vary from 7.9 to 53.5 Gm. per day and averaged 15.6 Gm. per day, or about five times the average control value.

This increased excretion of fat readily was shown to be of dietary origin. One of the 3 patients was given a fat-free diet for fourteen days, during which time his fecal lipid output fell from 39 to 6 Gm. per day. The addition at that time of 40 Gm. of fat to his diet was followed immediately by excretion of about 34 Gm. of lipid per day.

As the cause of the steatorrhea, the following factors were considered:

1. Intestinal motility: Since the patients lacked a stomach, they no longer had a proper regulatory mechanism for the flow of food through the intestines. However, it was found that a patient who had undergone a subtotal gastrectomy but who retained the pyloric third of the organ likewise excreted abnormally large amounts of fecal fat (from 13 to 18 Gm. per day). Furthermore, roentgenographic examination of the 3 patients who had undergone total gastrectomy did not reveal abnormally increased intestinal motility. In 2 of the 3 patients small intestinal pouches with a capacity of about 200 cc. were observed.

2. Lack of gastric secretion: The steatorrhea was also explained as being due to a lack of gastric secretion. This explanation, however, probably was not valid, for although the patient who underwent a subtotal gastrectomy had a considerable loss of fat in his stools, he did have normal amounts of free and combined hydrochloric acid in his gastric juice. Moreover, the daily addition of 33 Gm. of stomach U. S. P. (as a source of antianemia intrinsic factor) daily for ten days to the diet of 1 of the patients who had undergone a total gastrectomy was not followed by any decreased excretion of fat.

3. Presence of gastric cancer: The possibility next was investigated that the previous existence of the gastric cancer had induced the development of steatorrhea. This theory, however, was not tenable, for the fecal excretion of lipid by a patient with a gastric cancer in situ was found to be within normal limits. This patient excreted from 5.2 to 8.9 Gm. per day while taking a diet which contained 90 Gm. of fat.

4. Deficiency of bile salts: A deficiency of bile salts in the intestines and consequent impairment of lipid absorption never was considered very seriously as a cause for the steatorrhea. None of the 3 patients who had total gastrectomy had had any operation on the biliary tract, none had acholic stools at any time and,

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Investigation 22:243, 1943. Rekers, P. E.; Pack, G. T., and Rhoads, C. P.: Metabolic Abnormalities in Patients with Cancer of the Gastro-Intestinal Tract: VI. Disorders in Digestion and Absorption in Patients Who Have Undergone Total Gastrectomy, Surg., Gynec. & Obst., to be published.

finally, the addition of 4 Gm. of bile salts per day to the diet of 1 of the 3 increased the daily excretion of fat from 22 to 33 Gm.

5. Pancreatic function: Of the numerous possible causes for the existence of steatorrhea, the most likely appeared to be an inability of the patients to digest the dietary fat for its proper absorption through the gastrointestinal mucosa. Unfortunately, it was not feasible to ascertain the validity of this hypothesis by direct measurement of neutral fat and of fatty acids in the stools. Evidence was provided, however, which strongly suggested that the patients subjected to total gastrectomy no longer were able to digest fat. This evidence consisted of the observation that the daily oral administration of 25 Gm. of pancreatic enzymes to 1 of the 3 patients reduced his fecal output of fat from 20 Gm. to the almost normal value of 7.5 Gm. per day. The withdrawal of the pancreatic enzymes from the diet was followed within a few days by the reappearance of the steatorrhea. These observations still are to be confirmed in other patients who have undergone gastrectomy. It is interesting to note that the daily administration of 6 Gm. of lipocain, a lipotropic material obtained from the pancreas, to 1 of the 3 patients for ten days was without effect on the steatorrhea.

6. Effect of dietary protein: There is some reason to believe that the absorption of one or another dietary constituent from the gastrointestinal tract may be influenced by their relative proportion in the diet. For that reason, the diet of the 3 patients with steatorrhea was supplemented for fourteen days with from 70 to 100 Gm. of protein in the form of cooked beef. In 2 of the 3 patients this increased ingestion of protein was followed by a fall in the fecal output of lipid from 13.0 and 12.0 Gm. to 3.4 and 6.8 Gm. per day. On the other hand, a single addition of 100 Gm. of dextrose to the diet of the 3 patients had no effect whatever on the severity of the steatorrhea.

In summary, of 3 patients subjected to total gastrectomy and 1 subjected to subtotal gastrectomy for the excision of gastric cancer, all suffered from steatorrhea. This steatorrhea apparently is related to the dietary content of fat, and possibly of protein, and to the fat-splitting pancreatic enzymes. It is especially interesting that no organic disease of the pancreas was suspected in these patients. Certainly it is conceivable that the loss of weight, the dyspeptic symptoms and perhaps an eventual deficiency of fat-soluble vitamins could be attributed to steatorrhea.

2. *Postoperative Hypoprothrombinemia*.—A study of the levels of prothrombin in the plasma of 25 patients with cancer of the lower part of the gastrointestinal tract who were subjected to surgical procedures revealed that in 19 instances the plasma prothrombin level had fallen to from 4 to 54 per cent of the preoperative concentration. Whereas preoperatively 18 patients had hypoprothrombinemia, within the first three days after operation this abnormality was noted in 24.<sup>27</sup>

Unfortunately, the hypoprothrombinemia of patients with cancer of the lower part of the gastrointestinal tract does not respond well to the parenteral administration of vitamin K. All of the 25 patients received intramuscularly from 4 to 6 mg. of menadione during the first ten postoperative days. At the end of this time, the plasma prothrombin levels increased moderately in 10 instances, did not change in 7 and actually decreased further in 8. Despite the fact that there was an elevation of the level of prothrombin in the plasma of 10 patients, 23 of the 25 (92 per cent) still had significant degrees of hypoprothrombinemia.<sup>27</sup>

Furthermore, it appears that the frequent hypoprothrombinemia in patients whose gastrointestinal cancer had been removed may persist for several months. In another group of 19 patients who were free of disease for from two months to ten years after the surgical excision of a gastrointestinal cancer, 6 still had



abnormally low plasma levels of prothrombin. The incidence of other hepatic abnormalities was considerably less than that of the persistent hypoprothrombinemia.<sup>12</sup>

3. *Postoperative Anemia*.—Although the degree and incidence of anemia in patients whose gastrointestinal neoplasms have been removed have been found to be less than in patients still bearing the tumors, a mild degree of anemia frequently may persist. This is especially the case in patients subjected to a gastric surgical operation. For 9 patients who underwent subtotal gastric resections and 3 who underwent total resections six months to ten years previous to this study, the mean hemoglobin content was found to be 75.5 per cent with a range of from 63.3 to 87.7 per cent. The mean average red cell count was 3,910,000, with a range of from 3,320,000 to 4,350,000. Of all the 12 patients, 6 had a hemoglobin content below 80 per cent, 3 had a red cell count below 4,000,000 and 2 had macrocytosis.

The fact that the mean hemoglobin content and the red cell count of the patients who have undergone gastric resection are greater than those of the patients whose cancer has not been removed suggests some improvement in hemopoiesis.

#### CONCLUSIONS

In conclusion, then, it would appear that patients with gastrointestinal cancer suffer from several metabolic abnormalities which may endanger their operative and postoperative course. Many of these abnormalities probably are related to hepatic insufficiency, which probably is induced by the very presence of the gastrointestinal neoplasm. The removal of the cancer often is followed by a disappearance of the metabolic dyscrasias, principally that which involves the fabrication of serum protein. However, other dysfunctions, of which hypoprothrombinemia is the most prominent, persist well into the postoperative period. Total, and perhaps subtotal gastric resection, although necessary for the surgical treatment of the patient, may institute a new metabolic disturbance—steatorrhea and consequent loss of weight.

A proper recognition of these preoperative and postoperative complications should be necessary for the best treatment of the patient with gastrointestinal cancer. While it may be impossible at the present time to counteract all of these abnormalities, many can be corrected in time to prevent serious consequences.

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# MISTAKES AND MISUNDERSTANDINGS IN THE ROENTGENOLOGIC DIAGNOSIS OF GASTRIC CANCER

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Lest any one misapprehend the purpose of this paper, let it be said at the outset that what follows is not designed to be a defense of the roentgenologic method or an apology for its shortcomings. Neither is needed, for the general efficiency and reliability of roentgenologic examination in disclosing and identifying cancer of the stomach cannot be impugned, and it is safe to say that no practitioner of modern medicine would consider any diagnosis or exclusion of cancer to be complete and convincing without the roentgenologic opinion. Yet there are real errors, such as failures to discover lesions or to predict their true character, and apparent errors, which in fact are only misunderstandings as to the implications of certain roentgenologic reports. Although the proportion of these actual and fancied lapses is not large, they are sometimes made the basis of expressed or implied criticism that from the viewpoint of the roentgenologist does not appear to be fair or constructive. From one angle of view such criticism might be regarded as complimentary, in that it may imply expectation of perfection in the roentgenologic diagnosis of cancer. But the roentgenologist does not lay any claim to infallibility and is more than willing to point out his mistakes, whether proved or imagined, in the hope of promoting a frank and clear understanding with his clinical and surgical colleagues.

One variety of error that is utterly indefensible is failure to discover any existing gastric cancer, whatever its size, situation or morphologic characteristics may be. Roentgenologic examination will exhibit any gastric lesion that is capable of producing symptoms or that can be seen macroscopically, and failure to discern it should be charged to the examiner, not to the method. Even so, cancers occasionally are overlooked, not only by novices but by thoroughly experienced examiners, and extensive lesions as well as small ones may escape discovery. Most of these errors arise from a small but potent cause—a moment's distraction during the process of examination or neglect to apply a minor technical detail—the inevitable human negligence like that which sometimes results in a missed clinical diagnosis or needless fatality from operation.

Clinicians and surgeons, knowing as they do that roentgenologic methods are capable of demonstrating cancers having a diameter of only a few millimeters, doubtless wonder how any gross cancer could elude even the most casual roentgenologic inspection. It is true that the large, soft cancers deform the stomach so much that their presence should always be obvious; but scirrhus cancer, even though fairly extensive, may not distort the lumen noticeably, and unless the examiner studies the mucosal relief he may not discover the lesion. Often a cancer of the cardia will not be discovered unless the region of the gas bubble is inspected closely. However, while an explanation for some errors of omission can be offered, none are really excusable, and in extenuation it can be said only that they are relatively rare, for probably less than 1 per cent of cancers pass unseen when roentgenologic methods are employed.

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More common are the failures, mistakes and misunderstandings in the roentgenologic differential diagnosis of cancer from benign lesions. Small lesions in the juxtapyloric segment of the stomach are notoriously hard to identify specifically, and they account for most of the incomplete diagnoses of gastric disease. Hypertrophy of the pyloric muscle, hypertrophic rugae, some duodenal ulcers, benign gastric ulcer with accompanying spasm and small prepyloric cancers all produce elongation and narrowing of the pyloric canal, so that all these lesions and conditions look much alike. Hypertrophy of the pyloric muscle or of the antral rugae usually can be distinguished and specifically diagnosed. It might be supposed that recognition or exclusion of duodenal ulcer would also be easy, for roentgenologic examination is particularly reliable in this field, but in occasional instances the duodenal bulb is so markedly narrowed directly or indirectly by the ulcer or so inadequately filled with barium that the situation of the pylorus cannot be determined and the examiner cannot tell whether the lesion is prepyloric or postpyloric and hence is unable to predict its nature. Such duodenal ulcers, together with the prepyloric gastric ulcers and cancers, many of which cannot be identified confidently or at all, often oblige the examiner to return a nonspecific diagnosis of "lesion at the outlet." He thus assumes that his colleagues are aware of the reasons for his lack of precision and will appreciate the fact that the diagnosis is positive at least as to the existence of disease and its juxtapyloric situation. Furthermore, if he attempts to distinguish malignant from benign prepyloric lesions and errs, he expects the error to be regarded tolerantly.

But the aggregate of incomplete and wrong diagnoses is small in comparison with the number of misunderstandings by clinicians and surgeons as to the reservations implicit in certain roentgenologic diagnoses and reports. Most of these misunderstandings arise from diagnoses of benign tumors of the stomach and gastric ulcer and reports as to the operability of gastric cancers.

Benign intragastric neoplasms commonly have gross characteristics that favor roentgenologic identification, for most of them are smoothly ovoid polyps with only superficial ulceration, if any, and thus contrast strongly with the malignant tumors, which usually have noticeably irregular surfaces produced by deep ulceration and are not often pedunculated. Although the essentially nonmalignant new growths are made up principally of adenomatous, fibrous or other benign tissues, thorough sectioning and microscopic examination often reveal a limited region in which there are malignant cells. The roentgenologist feels warranted in diagnosing such tumors as benign because they are chiefly so, and he assumes that the rather common presence in them of localized malignant cells will not be forgotten by his consulting colleagues; on the other hand, the pathologist who discovers the malignant element has reason to feel that this is much more important than the general composition of the neoplasm and he is likely to return a diagnosis of cancer without further qualification. Thus, on the basis of the formal record the roentgenologist is chargeable with a definite error, and it will so appear in subsequent statistical reviews.

Small ulcerating cancers, malignant ulcers and benign ulcers of the stomach resemble each other strongly, especially after excision. However, the roentgenologist can identify most of the ulcerating cancers by their persisting remnants of tumefaction and their pseudoniches which do not penetrate into the gastric wall. Likewise, he can recognize many of the malignant ulcers because they are unduly large, or have irregular, insensitive craters, and are not accompanied by spasm. The third variety of ulcerous lesion, benign ulcer, has a rather regularly hemispheric true niche that is sculptured in the gastric wall, is surrounded by distorted or convergent rugae, is sensitive to pressure and usually gives rise to gastrospasm. All

such ulcers are diagnosed by the roentgenologist as gastric ulcers, without any qualifying adjective but with the implication that as no marks of malignancy were discerned the ulcers are probably benign, although malignancy cannot be excluded positively. The fact that 10 per cent or more of gastric ulcers are found microscopically to be malignant has been publicized thoroughly and the roentgenologist feels that his diagnoses have not been misleading, for he assumes that every ulcer will be considered as potentially malignant until proved innocent.

To surgeons and clinicians the misunderstood or partly mistaken diagnoses of benign tumor and gastric ulcer are likely to be surprising and vexatious; knowing the capabilities of the roentgenologic method, these consultants are perplexed at its apparent fall from grace and are inclined to wonder if the roentgenologist is capricious and inconsistent in his interpretations.

But, of course, the roentgenologist cannot afford to be temperamental in judgment and is obliged to draw his conclusions logically and consistently from objective signs alone, for he has learned from experience that only in that way can the greatest proportion of correct diagnoses be obtained. He is just as keenly solicitous as his colleagues that no operable cancer shall escape identification and is well aware that in about two thirds of the cases of gastric lesions in which surgical exploration is performed, the lesion is found to be malignant, but he is rightly unwilling to label any lesion as cancerous unless there is an adequate roentgenologic basis for that diagnosis. Most of the resulting misunderstandings or so-called errors could be avoided by adding to every roentgenologic diagnosis of benign tumor the caution that many such tumors are partly malignant, and to every diagnosis of gastric ulcer the warning that about a tenth of gastric ulcers, even though they may appear roentgenologically to be benign, turn out to be cancerous, but such reports would not be complimentary to the intelligence of other consultants.

Another prolific source of outright errors, inaccuracies and misunderstandings is the roentgenologic estimate as to the probable resectability in cases of gastric cancer, for circumstances combine to handicap this effort of the roentgenologist to be helpful. Chief among such handicaps is the fact that the resectability in a case of gastric cancer depends primarily on the skill, courage and personal equation of the surgeon concerned with the case, rather than on the various qualities, complications and roentgenologic characteristics of the growth. Thus, a cancer that would be regarded by one surgeon as utterly inoperable would be considered by another to be fairly resectable. Hence, the roentgenologist's opinions as to resectability, unless he is familiar with the abilities and customs of the surgical consultant, are likely to be disapproved and criticized by the latter. However, resectability, which connotes the utility and advisability of attempting resection, is not determinable solely on a subjective basis but is largely dependent on objective factors, such as the situation and extent of the growth, the invasion or non-invasion of structures adjacent to the stomach and the presence or absence of metastasis. Concerning most of these elements roentgenologic examination usually can elicit significant data and on these data, together with the examiner's knowledge of current surgical practices, the opinion as to resectability is based.

For many years it was considered commonly that, because of technical difficulties, cancer of the cardiac portion of the stomach or cancer extending into this segment from below could not be removed. Today, with modern surgical technics, the left costal arch is no longer an insuperable barrier, and some surgeons often remove cancer of the cardia unless the esophagus is implicated or other deterrents exist. If the surgeon is familiar with and skilful in the use of the transthoracic approach, he can remove cancer involving the cardia and lower part of the

esophagus. However, surgeons who prefer to limit their resections to cancer in the pyloric half of the stomach continue to be interested in the proximal limit of the growth. This the roentgenologist tries to determine, but although he makes liberal allowances for extension beyond that depicted, his estimate often falls short. Fixation or restricted mobility of the growth, indicative of its extension or inflammatory attachment to structures outside the stomach, often is determinable and is an obstacle but not always a definite bar to resection. Metastasis to abdominal lymph nodes is an extremely common cause of abandoning the projected removal of cancer reported roentgenologically as apparently resectable. That roentgenologic methods will not disclose such metastasis should be well known by this time, and it is unfair to charge that limitation of the method as an error on the part of the roentgenologist.

As a result of these circumstances, half or more of the cancers that appear roentgenologically to be resectable prove on exploration to be inoperable, often to the annoyance and surprise of medical and surgical consultants, although the roentgenologist repeatedly has admitted his limitations in this field. In view of the facts it would seem advisable for the roentgenologist to cease reporting general conclusions as to resectability in any case of gastric cancer, unless he is acquainted intimately with the views and practices of all other consultants in the case. In the absence of such acquaintance, the factual roentgenologic observations, without any deductions, might well be recorded or else reported and canvassed at a conference of the medical advisers. At all events, roentgenologic data are becoming less important in determining resectability, for exploration, which alone can definitely confirm or negate the diagnosis and settle the question of radical or palliative operation, is being recommended or demanded with steadily increasing frequency.

It is noteworthy that the roentgenologist rather seldom diagnoses benign lesions as malignant or resectable cancers as inoperable, and complaints on this score are rare. Thus the predominance of mistakes in the opposite direction may seem to indicate that he is prejudiced in favor of the benignancy of gastric diseases and the resectability of cancer. As a matter of fact, his prejudices, if he entertains them at all, would swerve him the other way, for he knows that most gastric lesions are malignant and most cancers inoperable. Perhaps the chief reason for his failures—and successes—is his strict adherence to the diagnostic codes and differential criteria that hard experience has taught him. If that is true, he will probably continue to make mistakes, or be accused of them, until he learns more about his art, or until his clinical and surgical associates learn more about it.

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# GASTROSCOPIC DIAGNOSIS OF GASTRIC CANCER

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The flexible gastroscope has come into widespread use, and reports attesting to its value in the diagnosis of gastric disease are numerous. In cases of gastric carcinoma it enables the examiner not only to detect the presence of the tumor but to determine its location, character and extent. On the other hand, it is of value in excluding the presence of gastric cancer in certain suspected cases, thus frequently preventing unnecessary operation. In this way Taylor<sup>1</sup> believed that he had probably averted an exploratory laparotomy in 25 of 68 suspected cases.

Unfortunately, gastroscopic examination may fail or prove unsatisfactory in some patients with gastric cancer. Obstruction at the cardia may prevent the examiner from introducing the instrument. Necrotic material, blood or barium sulfate may obscure visibility in the presence of pyloric obstruction. Spasm "ahead of the tumor" may occasionally conceal the lesion when located in the antrum.<sup>2</sup> There may be no visibility in cases of linitis plastica owing to inability to inflate the stomach. Furthermore, the lesion may be entirely overlooked when situated in one of the so-called blind areas. These comprise part of the cardia, part of the fundus, the upper part of the lesser curvature,<sup>3</sup> the upper part of the posterior wall, the lesser curvature and adjacent posterior wall of the antrum and part of the greater curvature where the tip of the instrument impinges on the gastric wall.

I have to a certain extent attempted to follow Borrmann's macroscopic classification of gastric cancer into four types, as advocated by Schindler.<sup>4</sup> The first, or polypoid, type is a lobulated tumor projecting into the lumen of the stomach, with an irregular, lumpy surface which may be hemorrhagic or ulcerated. The second type comprises the malignant ulcer, usually shallow, with a raised, everted edge and a floor which is usually sloughing and brown, dark red, dirty gray or, less frequently, white. This contrasts with the usually deep crater, sharp, often partly undermined edge and white base of the benign ulcer. Type 3 carcinoma consists of an ulcer in which part of the wall is missing because the lesion has infiltrated the surrounding mucosa. I have had much difficulty in determining this type gastroscopically. This may be due in part to inability always to see the entire border of a malignant ulcer even when it is intact. The fourth type is the infiltrating lesion

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1. Taylor, H.: Practical Evaluation of Gastroscopy (Hunterian Lecture), *Lancet* 1:131 (Feb. 1) 1941.

2. Walters, W.: Surgical Treatment of Ulcerating Gastric Lesions, with Correlated Roentgenologic Studies, *Am. J. Roentgenol.* 43:819 (June) 1940.

3. F. E. Templeton and R. C. Boyer (The Diagnosis of Gastric Cancer: An Analysis of the Gastroscopic and Roentgenologic Findings, *Am. J. Roentgenol.* 47:262 [Feb.] 1942) recently emphasized the fact that 15 of 22 (benign) gastric ulcers which were visible in the roentgenogram but not on gastroscopic examination were situated "on or near the lesser curvature about half way between the gastric angle and esophageal orifice."

4. Schindler, R.: Early Diagnosis of Cancer of the Stomach: Gastroscopy and Gastric Biopsies, Gastrophotography and X-Rays, *J. Nat. Cancer Inst.* 1:451 (Feb.) 1941.

with rigidity or reduction of the gastric lumen which may not be affected by inflation. The mucosal surface appears grayish and nodular and is usually not ulcerated. It may be difficult to differentiate this type of tumor from hypertrophic gastritis, syphilis, lymphosarcoma or leukemia. Like Schindler, I have found that the majority of cases are of the diffuse infiltrating type. For excellent illustrations of the gastroscopic appearance of gastric cancer, the reader is referred to the books of Schindler<sup>5</sup> and Moutier.<sup>6</sup>

According to Schindler<sup>4</sup> type 1 carcinoma grows slowly and type 2 metastasizes late, while the prognosis of types 3 and 4 is relatively much less favorable in spite of early surgical intervention. My own experience is as yet insufficient to permit of any conclusions along these lines.

My experience with gastroscopy is limited to the use of the flexible gastroscope and is based on 1,366 examinations made since April 1936. I have used the gastroscope to examine (one or more times) 95 patients with gastric cancer, for 78 of whom the diagnosis was verified by either operation or autopsy.

TABLE 1.—*Analysis of Gastroscopic Examinations in Seventy-Eight Proved Cases of Gastric Cancer*

	Number of Cases
Examination unsatisfactory:	
Resistance at cardia.....	4
Tumor obscured by gastric contents.....	5
Linitis plastica preventing inflation of stomach.....	1
Total.....	10
Tumor entirely overlooked:	
In prepyloric region.....	5
High on posterior wall.....	1
Total.....	6
Tumor mistaken for another type of lesion.....	9*
Tumor correctly diagnosed .....	53

\* In 2 of these cases the lesion was correctly diagnosed on subsequent examination.

#### RESULTS OF EXAMINATIONS

Analysis of the examinations in the cases in which the diagnosis was proved is given in table 1.

*Examination Unsatisfactory.*—Resistance at the cardia was apparently due to direct encroachment of the neoplasm. This type of resistance does not always indicate the presence of organic obstruction, as it may be due to spasm. Occasionally, when there is no obstruction at the cardia, by waiting a few moments and manipulating the instrument in a most gentle fashion one may help it slip into the stomach. It is also possible that no resistance will be encountered if the examination is repeated on another day. Retained gastric contents usually consisted of necrotic or grumous material. In an instance of pyloric obstruction barium sulfate was still present in the stomach five days after it had been administered by the roentgenologist. Schindler<sup>5</sup> has emphasized the inability to inflate the stomach in cases of linitis plastica, an occurrence which should per se suggest

5. Schindler, R.: *Gastroscopy: The Endoscopic Study of Gastric Pathology*, Chicago, University of Chicago Press, 1937.

6. Moutier, F.: *Traité de gastroscopie et de pathologie endoscopique de l'estomac*. Paris. Masson & Cie. 1935.

the presence of this lesion. However, I had such an experience with a patient with antral carcinoma, in whom during a second examination made a week after the first the stomach was readily distensible. The initial failure was probably due to spasm. Experience has emphasized the importance of repeating the gastroscopic examination when it proves unsatisfactory or inconclusive.

TABLE 2.—*Proved Cases of Gastric Carcinoma in Which Lesion Was Misinterpreted on Gastroscopic Examination*

Number	Patient	Gastroscopic Diagnosis	Comment
1	J. R.	Benign ulcer.....	Sharply defined border; whitish base
2	P. N.	Benign ulcer.....	Temporary healing; correct diagnosis in 3 of 4 examinations
3	L. K.	Benign ulcer.....	Border sharp; base white and deep; temporary healing
4	P. V.	Benign ulcer.....	Entire lesion not seen
5	J. S.	Benign ulcer.....	Base white; border sharply defined
6	M. H.	Duodenal ulcer (presumptive)	Antral distortion misleading
7	D. D.	Hypertrophic gastritis.....	Changes characteristic
8	J. C.	Hypertrophic gastritis.....	Large, rigid folds
9	C. W.	Superficial gastritis.....	Malignant changes at first obscured (or overlooked); diagnosis made subsequently

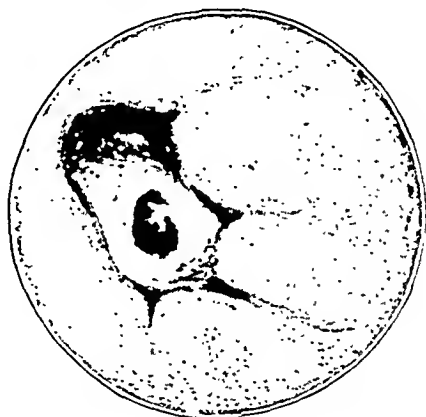


Fig. 1.—Photograph of a drawing of an ulcer (case 1, table 2) made at gastroscopic examination, with all the characteristics of a benign lesion (sharp border, deep crater, white base, with a small clot near the center and swollen radiating rugae). The growth was found to be malignant ten months later.

*Tumor Entirely Overlooked.*—Overlooking of a tumor was due to its location in a well recognized blind area, namely, the prepyloric region (generally lesser curvature of the antrum) or the posterior wall near the cardia.

*Tumor Mistaken for Another Type of Lesion.*—It is of much interest that the carcinoma (malignant ulcer type) was most commonly mistaken for a benign gastric ulcer (table 2). This only emphasizes the fact that the proof of the benign or malignant character of an ulcer is in the histologic examination (fig. 1). In this connection I should like to point out that temporary healing was striking in 2 of the cases of malignant ulcer (fig. 2), a characteristic which has already been emphasized by a number of observers.<sup>7</sup> In 3 cases the neoplasm was mistaken for

7. Palmer, W. L.: Benign and Malignant Gastric Ulcers: Their Relation and Clinical Differentiation. *Ann. Int. Med.* 13:317 (Aug.) 1939. Eusterman, G. B.: Carcinomatous Gastric Ulcer: Misleading Results of Medical Therapy, *J. A. M. A.* 118:1 (Jan. 3) 1942. Taylor.<sup>1</sup>



gastritis. Schindler<sup>8</sup> has pointed out the difficulty in distinguishing infiltrating types of gastric carcinoma from hypertrophic gastritis. In this connection it is hoped that a biopsy forceps of the design proposed by Kenamore<sup>9</sup> may prove helpful.

#### COMMENT

Gastric lesions other than primary cancer may be mistaken for gastric carcinoma (table 3). Mistaking a pancreatic carcinoma eroding the stomach for a primary gastric tumor is readily understandable. This also applies to ulcerated neurilemmoma. With lymphosarcoma the presence of large stiff folds should aid identification (fig. 3). It is not surprising that a benign ulcer should be mistaken for a malignant one, since the reverse is true. Because of the frequent association of

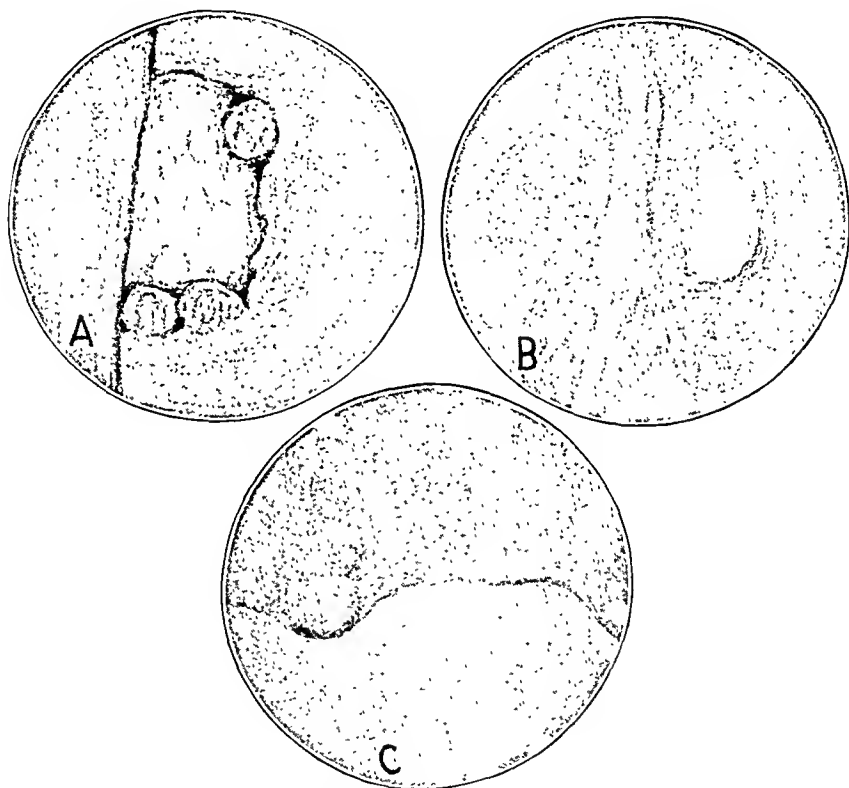


Fig. 2.—Photographs of drawings of case 2, table 2. *A*, the ulcer was considered malignant on the first examination (Nov. 13, 1939) because of the nodules in its border. *B*, on the second examination (Dec. 4, 1939) it was regarded as benign because of the marked healing. *C*, it was obviously diffusely infiltrating in character on the last examination (March 4, 1940).

atrophic gastritis and gastric cancer, the presence of this type of gastritis in case 11 wrongly influenced me in the diagnosis of malignant ulcer. Experience has since confirmed the coexistence of atrophic gastritis and benign gastric ulcer.<sup>10</sup> Schindler<sup>11</sup>

8. Schindler, R.: Gastritis Simulating Tumor Formation, *Am. J. Digest. Dis.* **6**:523 (Oct.) 1939.

9. Kenamore, B.: A Biopsy Forceps for the Flexible Gastroscope, *Am. J. Digest. Dis.* **7**:539 (Dec.) 1940.

10. Maher, M. M.; Zininger, M. M.; Schiff, L., and Shapiro, N.: Some Observations on Gastritis and Peptic Ulcer, *Am. J. M. Sc.* **205**:328 (March) 1943.

11. Schindler, R., and Arndal, O.: Gastroscopic Differential Diagnosis of Benign and Malignant Ulcer of the Stomach, *Arch. Surg.* **44**:473 (March) 1942.

very recently reported it in 19 of 79 cases. Relatively little is known about the gastroscopic appearance of gastric syphilis. Confronted with the same gastroscopic findings as those of W. N. (table 3), I should again make the diagnosis of gastric

TABLE 3.—Cases of Histologically Proved Lesions Mistaken for Gastric Carcinoma on Gastroscopic Examination

Number	Patient	Lesion Present	Comment
1	C. J.	Carcinoma of pancreas eroding stomach	.....
2	R. H.	Carcinoma of pancreas eroding stomach	.....
3	A. D.	Carcinoma of pancreas eroding stomach	.....
4	A. P.	Ulcerated neurilemmoma.....	Simulated malignant ulcer
5	H. E.	Lymphosarcoma.....	Simulated malignant ulcer
6	R. B.	Benign gastric ulcer.....	Mistake due to inexperience
7	F. K.	Benign gastric ulcer.....	Base blackish
8	W. R.	Benign gastric ulcer.....	Lesion elevated; base necrotic, nodular
9	R. H.	Benign gastric ulcer.....	Everted, nodular border
10	A. K.	Benign gastric ulcer.....	Base blackish; border elevated and irregular
11	H. G.	Benign gastric ulcer.....	Lesion seen tangentially; atrophic gastritis present
12	C. F.	Duodenal ulcer.....	Antral distortion misleading
13	W. N.	Gastric syphilis (ulcerative)...	Necrotic base; adjacent (nodular) gastritis misleading

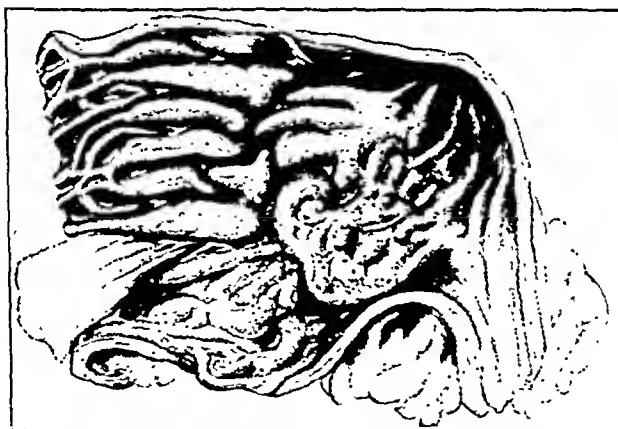


Fig. 3.—Photograph of a drawing of a portion of the stomach (case 8, table 2) in which large stiff folds were due to diffuse adenocarcinoma.

carcinoma. Hence it may occasionally be useful to await the results of antisyphilitic therapy before advising operation.

In spite of its limitations, gastroscopy may be of much value in the diagnosis of gastric carcinoma.<sup>12</sup> For example, it was the sole method of revealing the presence of the tumor in 7 of my proved cases, in 6 of which the growth was operable. It has not infrequently been of aid in indicating the spastic nature of roentgenologic defects, through failure to reveal an organic lesion. It has also demonstrated the benign character of gastric ulcer or hypertrophic gastritis roentgenologically interpreted as malignant. Sometimes it revealed the upper limits of the tumor more accurately than the roentgenogram, thus helping the surgeon to determine preoperatively the extent of resection necessary.

While the gastroscope may be more helpful than the roentgenogram in the diagnosis of gastric cancer in some cases, the converse is more frequently true. In 11 of my patients the roentgenogram was the sole means of revealing the presence

12. Benedict, E. B.: Gastroscopic Observations in Neoplasm, *New England J. Med.* **214**: 563 (March 19) 1936. Taylor.<sup>1</sup> Schindler.<sup>4</sup>

of the tumor. I agree with Templeton and Boyer,<sup>3</sup> who stated that by the use of both methods the percentage of correct diagnoses will be higher than by the use of either method alone.

In looking through a gastroscope the clinician should constantly bear in mind that he is viewing only part of the mucosal surface of the stomach, not its entire surface nor its deeper layers or surrounding structures. It is only by weighing the information he thus obtains with the evidence he collects from the history and physical, roentgenologic and other examinations that he will most frequently arrive at a correct diagnosis.

#### SUMMARY

In 53 (and subsequently 55) of 78 proved cases of gastric cancer the lesion was seen and correctly diagnosed through the flexible gastroscope. In 7 cases gastroscopic examination was the sole means of revealing the presence of the tumor. In 10 of the cases the examination was unsatisfactory because of failure to introduce the instrument or poor visibility. In 6 additional cases the lesion was situated in a "blind area" and was not seen. In 9 instances it was mistaken for another type of lesion, most commonly a benign gastric ulcer. In 13 cases selected from a miscellaneous group, lesions proved histologically to be other than primary gastric carcinoma were mistaken for gastric cancer.

Dr. Nathan Shapiro assisted in the compilation of data for this article.

# SURGICAL CARE OF PATIENTS WITH GASTRIC CANCER BEFORE AND AFTER OPERATION

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The preoperative preparation and the postoperative care of patients with carcinoma of the stomach have assumed increasing importance during the past decade, and during this period there has been a steady decline in the mortality associated with radical gastric resection. The importance of the nonoperative phases of management is now so clearly understood that no surgeon interested in this type of surgery would consider operation without at least attempting to correct certain of the abnormalities which exist in nearly every instance when the patient comes for resection.

## THE PATHOLOGIC PHYSIOLOGY OF GASTRIC CANCER

The parietal cells of the gastric mucosa normally secrete hydrochloric acid at a concentration of about 165 millimols or 0.6 per cent. A variety of mechanisms are probably involved in the process of neutralization, so that the actual acidity of the gastric contents varies widely in the same person from time to time and in different persons. It should be remembered that when complete absence of hydrochloric acid, the true anacidity of Keefer and Bloomfield,<sup>1</sup> is demonstrated in a patient, there is also nearly always an absence of the gastric enzymes, pepsin and rennin.

Carcinoma of the stomach is usually associated with a low level of gastric acid, or complete anacidity, and at the same time a lowered volume of secretion. As a general rule the gastric contents, even in the patient with a moderately early carcinoma of the stomach, become foul. This is very likely in large part due to the action of bacteria on ingested food, a mechanism which comes into play in hypochlorhydria and even more in achlorhydria. The concentration of gastric acid is normally sufficient to prevent the growth of the common pathogenic organisms which may gain access to the stomach in food. When, however, the free hydrochloric acid, which forms the major component of the gastric acid, is reduced in concentration or is completely absent, the stomach contains bacteria in abundance and in considerable variety. The common inhabitants of the oropharynx can soon multiply in fertile soil when they are not exposed to the inhibiting and destructive effects of the free acid and enzymes of the stomach.

The dilatation of the stomach is as a rule due to two factors. (1) the obstructing lesion and (2) the existence of a subclinical or clinical deficiency of the vitamin B complex. The retrograde distention resulting from a slowly increasing obstruction requires no further discussion. It occurs in any hollow viscus proximal to an obstructing lesion.

From Surgical Service B of the Hospital of the University of Pennsylvania and the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania.

1. Keefer, C. S., and Bloomfield, A. L.: Bull. Johns Hopkins Hosp. 39:304, 1926.

The dilatation associated with the deficiency of the vitamin B complex results in large part from the atony of the gastric musculature, which is present in an increasing degree as the deficiency is extended. As the obstruction becomes more evident and the digestive symptoms become more pronounced, the patient usually changes from a well balanced diet to one which contains an excess of carbohydrates, and the final result is pronounced anorexia and loss of weight. If the carbohydrate content of the diet is increased the requirements of vitamin B<sub>1</sub> become greater, and if they are not met a clinical or subclinical deficiency soon occurs. Thus the anorexia becomes even more pronounced and the nutritional condition of the patient suffers still further. While occasionally the edema observed in some of these patients may be of the type associated with beriberi, it is in our opinion more usually due to the hypoproteinemia which so many of the patients have.

The nausea and anorexia so frequently observed in gastric carcinoma are in part associated with a deficiency of the vitamin B complex. The studies of Hueblein, Thompson and Scully,<sup>2</sup> made in this laboratory, demonstrated that in the presence of a B complex deficiency gastrointestinal tone and pattern did not return to normal regardless of the amount of thiamine chloride which was administered. Even the administration of riboflavin and nicotinic acid failed to restore the roentgenograms to normal, but they did become normal after the patient took brewers' yeast. In deficiency of the vitamin B complex the gastric outline is enlarged and the gastric walls are smooth. These are in fact important diagnostic criteria. When dilatation is present without a deficiency of the vitamin B complex the fluoroscopist will nearly always observe evidences of increased peristaltic activity of the gastric wall. A decrease in tonus and impairment of peristaltic activity indicate a superimposed deficiency of the vitamin B complex.

The anorexia and nausea from which these patients may suffer result in a restriction in total caloric intake on the one hand and in an alteration in the composition of the ingested food on the other. The two conditions, lowered total caloric intake and a coincidental reduction in the ingested protein, bring about a reduction in the concentration of plasma protein. There results a subclinical or clinical nutritional edema.

The hypoproteinemia, or more specifically the hypoalbuminemia, which so many of these patients have is much more common than it is generally supposed to be. It is at times masked by the coexisting dehydration but becomes evident when attempts are made to correct this. The edema which may be precipitated when attempts are made to restore the fluid balance is greatly accentuated when sodium chloride is given intravenously. There occurs not only evidence of superficial subcutaneous edema but a widespread edema of the gastrointestinal tract. The underlying basis for this state is the same, a reduction in ingestion and utilization of protein, with a subsequent reduction in the concentration of plasma protein and a decrease in the colloid osmotic pressure of the blood. Thus the mechanism for holding fluids in blood vessels becomes disturbed. In a similar manner the mechanism for drawing fluids back into the blood vessels is deranged, and the edema associated with trauma, such as occurs at any site of resection and anastomosis, is accentuated and prolonged. As Weech and Ling<sup>3</sup> have shown, the administration of large amounts of sodium chloride or sodium bicarbonate increases retention of fluid when the concentration of serum albumin is below normal. This must always be kept in mind in the postoperative period.

2. Hueblein, G. W.; Thompson, W. D., Jr., and Scully, J. P.: *Am. J. Roentgenol.* 46: 866, 1941.

3. Weech, A. A., and Ling, S. M.: *J. Clin. Investigation* 10:869, 1931.

Jones and Eaton<sup>4</sup> first pointed out the frequency of postoperative nutritional edema, and Mecray, Barden and Ravdin<sup>5</sup> have shown that the emptying time of the normal stomach is greatly increased as the concentration of plasma protein is decreased and that it returns to normal as the concentration is by one means or another restored to a normal level.

Barden, Ravdin and Frazier<sup>6</sup> have shown that the edema following operation may be so pronounced as to mimic in every way a technical defect in the anastomosis, resulting either in a prolonged delay in gastric emptying or in nearly complete obstruction. The importance of recognizing this type of functional impediment to gastric emptying cannot be stressed too much. It is possible that the edema so frequently observed in these patients is not always entirely due to hypoproteinemia, although we believe this to be the most important single factor. A coexisting deficiency of vitamin B<sub>1</sub> or C may play a part in the production of the edema or may exaggerate the edema of simple hypoproteinemia. Regardless of the other factors involved, a concentration of the serum albumin below 3 Gm. per hundred cubic centimeters or of the total plasma protein below 5.5 Gm. per hundred cubic centimeters should be considered as greatly increasing the hazards of operation.

Thompson, Ravdin and Frank<sup>7</sup> have shown that the period of delay in fibroblastic proliferation of healing wounds is greatly increased in the presence of protein undernutrition. Lanman and Ingalls<sup>8</sup> have demonstrated marked interference with the laying down of collagen in healing wounds in the presence of a deficiency of vitamin C. Hartzell, Winfield and Irvin<sup>9</sup> in a study of patients with disruption of abdominal wounds showed that in nearly every instance the patients had hypoproteinemia, a deficiency of vitamin C or both. It can now be assumed that many of the wound disruptions which have been observed following operation for gastric cancer are due to biologic defects in the mechanisms which control tissue repair.

Not a few of the patients with gastric carcinoma have moderate or severe degrees of anemia. In most of these the anemia is of the so-called iron deficiency type, but in a few it assumes many of the characteristics of primary pernicious anemia, perhaps as the result of a disappearance from the stomach of the intrinsic factor.

#### PREPARATION OF PATIENTS WITH GASTRIC CANCER FOR OPERATION

The indications for therapy follow directly from knowledge and understanding of the pathologic physiology of gastric cancer. Therapy must be directed on the one hand toward correcting the infection, dilatation and atony which affect the stomach and on the other hand toward correcting the systemic changes which result from the nutritional deficits and the losses of fluid and electrolytes to which so many of the patients are subject.

For several days before operation the stomach should be kept empty. This may be accomplished by periodic gastric lavage or by continuous suction drainage plus repeated lavage. We prefer the latter method. Certain of these patients

4. Jones, C. M., and Eaton, F. B.: Postoperative Nutritional Edema, *Arch. Surg.* **27**: 159 (July) 1933.

5. Mecray, P. M.; Barden, R. P., and Ravdin, I. S.: *Surgery* **1**:53, 1937.

6. Barden, R. P.; Ravdin, I. S., and Frazier, W. D.: *Am. J. Roentgenol.* **38**:196, 1937.

7. Thompson, W. D.; Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption, *Arch. Surg.* **36**:500 (March) 1938.

8. Lanman, T. H., and Ingalls, T. H.: *Ann. Surg.* **105**:616, 1937.

9. Hartzell, J. B.; Winfield, J. M., and Irwin, J. L.: Plasma Vitamin C and Serum Protein Levels in Wound Disruption, *J. A. M. A.* **116**:669 (Feb. 22) 1941.

have pyloric obstruction of such a degree that great collections of undigested food, and even in certain instances phytobezoars, accumulate in the stomach. These accumulations plug up the usual nasal catheter, frustrating attempts at suction drainage. In such cases lavage should be carried out with an old-fashioned stomach tube of large caliber.

It is best not to give any food by mouth for from two to five days after the institution of suction drainage and only when pyloric patency is established to permit the ingestion of readily digestible foods.

The administration of small amounts of dilute hydrochloric acid during this period, as suggested by Harvey and Oughterson,<sup>10</sup> is, we believe, helpful. The acid can be introduced into the stomach through the indwelling tube, which is then clamped for from one to two hours. The use of hydrochloric acid will lead to an earlier disappearance of the foulness of the gastric contents and to a more rapid reduction in the bacterial count.

This regimen of local treatment leads to a considerable improvement in the state of the patient, a lessening of the epigastric distress and pain and a disappearance of the nausea and vomiting; frequently after continuance of the program there is evidence of improved gastric emptying.

*Administration of Vitamins.*—While the cleansing of the stomach is being carried out deficiencies of the important vitamins should be compensated. From 10 to 20 mg. of thiamine hydrochloride and 100 mg. of ascorbic acid may be given subcutaneously each day. As soon as evidence is obtained of a functioning pylorus, 2 to 4 Gm. of brewers' yeast should be given daily by mouth or through the stomach tube, the tube being clamped for two hours afterward. If this cannot be done for some time because the pylorus is not patent, a daily dose of 50 mg. of nicotinic acid amide may be given by the subcutaneous route.

Vitamin K, while not specifically indicated for all patients, has frequently been useful for those whose gastric drainage is at times blood tinged. In several of these patients mild to moderate degrees of hypoprothrombinemia have been found, and if this condition is present one of the soluble synthetic products with vitamin K activity should be given parenterally; 4-amino-2-methyl-1-naphthol hydrochloride (synkamin) in doses of 3 mg. per day is generally satisfactory.

The hypoprothrombinemia is often associated with hepatic metastases, but it should not be assumed that all patients with hypoprothrombinemia have inoperable lesions. Metastases to the liver have not been a constant finding at operation.

#### WATER AND ELECTROLYTE BALANCE

Nearly all patients of this group who have been vomiting and many others as well will have become dehydrated. There is no way of estimating the degree of the dehydration, though the observations of Maddock and Coller<sup>11</sup> that the clinical signs of dehydration indicate a loss of 6 per cent of body weight are often helpful. Thus a man weighing 80 Kg. who has sunken eyeballs, dry tongue and poor skin turgor may be assumed to have a negative water balance of 60 cc. per Kg., or a total of 4,800 cc. at least.

For several reasons, however, it may be unwise to attempt to replace this deficit too rapidly. A deficiency of serum proteins may lead to faulty distribution of fluid within the body. When a patient has such a deficiency, the addition of fluid dilutes the serum proteins further, and increased edema results. Also circu-

10. Harvey, S. C., and Oughterson, A. W.: *Ann. Surg.* **115**:1066, 1942.

11. Maddock, W. G., and Coller, F. A.: *Water Balance in Surgery*. J. A. M. A. **108**:1 (Jan. 2) 1937.

latory defects may impair the normal distribution of fluid in the body and increase the danger associated with the rapid infusions. The tolerance of each patient for fluid must be carefully watched but it is unreasonable to assume that the intravenous route cannot be used if care is exercised.

With the exception of patients with cardiac disease, we have found it practical to administer 50 to 60 cc. of fluid per kilogram of body weight per day to dehydrated patients over and above the amount lost by suction drainage. This is continued until the twenty-four hour output of urine exceeds 1,000 cc. When the kidneys excrete this amount it is generally assumed that dehydration has been overcome and the fluid intake can be reduced to maintenance levels.

At the same time that the water balance is being corrected the salt balance, the acid-base equilibrium and the serum protein concentration must be corrected. As has already been pointed out, the administration of water and sodium chloride to a patient without labile protein reserves, even if his serum protein concentration in the dehydrated state is normal, increases the tendency to edema and may occlude the pylorus completely in a patient whose pyloric canal is already narrowed by scar tissue.

Patients who have vomited repeatedly generally have a chloride deficiency. In calculating the amount of salt needed to correct this the formula of Collier, Bartlett, Bingham, Maddock and Pedersen<sup>12</sup> has generally been used.

For each 100 mg. per hundred cubic centimeters of reduction in the serum chloride concentration 0.5 Gm. of sodium chloride per kilogram of body weight is allowed. Here again experience has led us to correct the deficit fractionally. One-half the calculated dose may be given and subsequent dosage determined on the basis of another determination of the chloride concentration and with due consideration for the clinical course of the patient.

Occasionally a patient who does not respond to appropriate doses of physiologic solution of sodium chloride may respond if a 2 per cent solution is given intravenously.

Should hyperchloremia inadvertently be produced, excess salt may be removed fairly rapidly by gastric lavage. Two hundred cubic centimeters of water may be introduced into the stomach and aspirated after twenty minutes. Another 200 cc. is then introduced, and so on. The reduction in plasma chlorides by this method may be fairly rapid and should be carefully controlled.

We have sometimes encountered severe disturbances of acid-base equilibrium in patients with gastric lesions. Usually such disturbances are corrected by the body if ketosis is prevented and moderate amounts of physiologic solution of sodium chloride are provided. When this fails or when extreme changes are found which it is considered wise to correct quickly, sixth-molar sodium lactate solution may be used to increase the serum carbon dioxide. Two cubic centimeters per kilogram of body weight is usually required to produce an elevation of one volume per cent.

In cases of extreme alkalosis 2 per cent ammonium chloride solution has been given intravenously. Two cubic centimeters per kilogram of body weight of this solution depresses the carbon dioxide about 3 volumes per cent. The method has had too limited a trial to permit a statement regarding its safety, but it has been used successfully and without serious reaction with patients who did not respond adequately to administration of sodium chloride and for whom it was felt there was danger of nephrosis due to alkalosis (Zintel, Rhoads and Ravdin).<sup>13</sup>

12. Collier, F. A.; Bartlett, R. M.; Bingham, D. I. C.; Maddock, W. G., and Pedersen, S.: *Ann. Surg.* 108:769, 1938.

13. Zintel, H. A.; Rhoads, J. E., and Ravdin, I. S.: To be published.



## TREATMENT OF ANEMIA

If an anemia of considerable degree is present the patient should receive multiple small transfusions of whole blood. Should the anemia resemble primary pernicious anemia, parenteral administration of a suitable liver extract should be begun before operation. Subsequent to operation, when the new stoma is functioning, iron therapy should be instituted for those patients whose anemia is of the iron deficiency type.

Of all the various disturbances of patients with gastric carcinoma, possibly hypoproteinemia is the most difficult to correct. It should be remembered that after hypoproteinemia has persisted for some time the ability of animals to elaborate plasma proteins in the body becomes impaired (Whipple).<sup>14</sup> It has been our impression that this is also true in man. The most rapid and most satisfactory method is the transfusion of plasma. Usually the injection of 250 to 500 cc. per

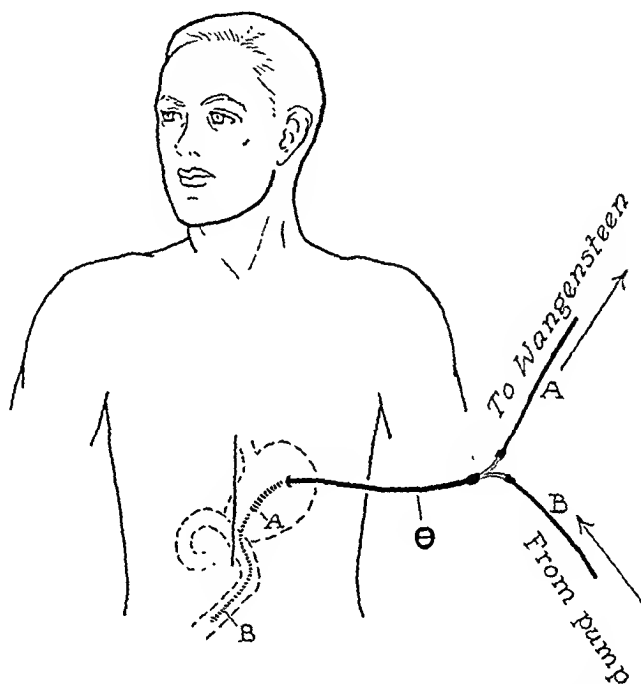


Fig. 1.—Diagram of the use of an Abbott-Rawson tube for gastric suction and jejunal feeding as suggested by Biscgard.<sup>16</sup> Such tubes should not be removed too early.

day will bring the serum protein level up to normal. Occasionally larger amounts may be required. There is some evidence that in man solutions of amino acids injected intravenously may be of value in maintaining nitrogen equilibrium. However, even the most favorable reports indicate that a relatively small fraction of this material is utilized for the production of serum proteins. In general, the effect of solutions of amino acids is too slow for them to be used in preparing the hypoproteinemic patient for operation. If preparations become available that may be given in larger amounts without reaction, they may come to play a much larger role.

Protein digests fed into the stomach or duodenum are also of value once pyloric patency is established. We believe that these digests are more readily utilized than are the protein complexes from which they are prepared.

14. Whipple, G. H.: *Am. J. M. Sc.* 196:609, 1938.

*Effect of a Preparation of Amino Acids, Polypeptides and Carbohydrates\*  
on Serum Protein Concentration (Orojejunal Route)*

Patient	Diagnosis	Total Amount, Gm.	Time, Days	Serum Protein, Gm./100 Cc.	
				Before	After
A. S.	Gastric cancer.....	97	3	5.70	5.99
R. S.	Gastric cancer.....	120	5	5.90	6.51
H. D.	Pyloric stenosis due to ulcer.....	240	3	6.77	7.25
M. K.	Pyloric stenosis due to ulcer.....	309	7	5.76	6.07
A. B.	Duodenal ulcer.....	500	4	6.07	6.20
W. C.	Pyloric stenosis due to ulcer.....	500	9	6.54	7.22
L. W.	Bleeding duodenal ulcer.....	500	4	7.21	9.44
L. S.	Gastric cancer.....	700	5	6.11	5.98
J. S.	Gastric cancer.....	900	5	6.25	6.51
L. G.	Gastric cancer.....	910	5	6.63	6.90

\* The preparation used was aminoids (Arlington Chemical Company).

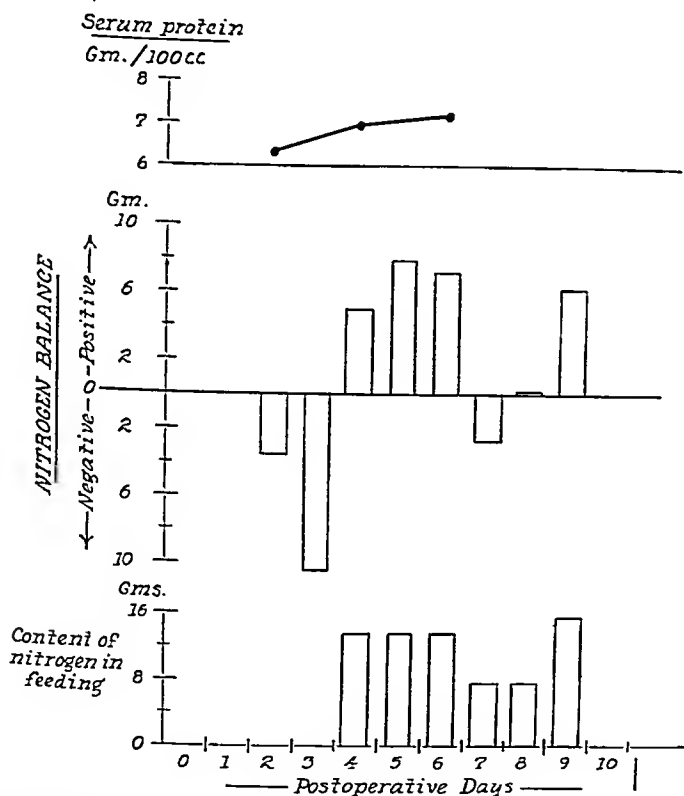


Fig. 2.—Nitrogen balance and serum protein concentration following the introduction of a mixture of banana powder and milk into the jejunum after gastric resection.

#### THE NUTRITION OF THE PATIENT AFTER OPERATION

After operation, the orojejunal feeding method described by Ravdin, Stengel and Prushankin<sup>15</sup> is very effective. This can be modified by placing the feeding tube through the gastric wall in the manner described by Bisgard<sup>16</sup> (fig. 1.) For a majority of the patients a preparation containing amino acids, polypeptides and carbohydrates has been employed in orojejunal feeding (table). However, simple foods, such as skim milk and banana powder, have been used successfully (fig. 2).

15. Ravdin, I. S.; Stengel, A., Jr., and Prushankin, M.: Control of Hypoproteinemia in Surgical Patients, *J. A. M. A.* **114**:107 (Jan. 13) 1940.

16. Bisgard, J. D.: *Surg., Gynec. & Obst.* **74**:239, 1942.

When this method of feeding is utilized the feeding mixture should not contain too much fat, for even though the mixture is placed in the jejunum gastric emptying will be delayed. Failure to recognize this fact has greatly increased the time of convalescence of many patients.

In the postoperative period the intravenously injected fluids must be carefully controlled. The amount of sodium chloride, of dextrose and water and of plasma or serum or amino acids which each patient should receive must be judged daily by a careful study of the previous day's intake and output, by repeated studies of the plasma chloride and protein and at times even of the total base. When the orojejunal method is instituted intravenous administration of fluids, with the occasional exception of plasma or serum, is rarely required.

The augmented intake of vitamins should by all means be maintained during the period of hospitalization and more especially during the period of wound healing. As soon as evidence is obtained of a functioning stoma, orojejunal tubes should be removed and food intake by mouth should be permitted.

#### CHEMOTHERAPY

Although they may not be essential, we have used sulfonamide compounds in the preoperative preparation of many patients with carcinoma of the stomach. The serious risk of spreading infection may in part be controlled by preoperative administration of a sulfonamide compound and by local implantation of crystalline sulfanilamide at the site of the resection and anastomosis.

#### CONCLUSION

Patients with operable carcinoma of the stomach require the most careful supportive treatment. During the preoperative period special attention must be given to the problem of overcoming dilatation of the stomach and infection of the gastric contents. The water balance, electrolyte balance and vitamin intake of the patients require constant attention both before and after operation.

The protein deficit which is so often present in patients having pyloric obstruction is best managed in our experience by transfusion before operation and by jejunal feedings after operation.

In this clinic the institution of the program which has been outlined has resulted in an earlier and more satisfactory preparation of the patient, in a shorter convalescence from the operation and in a reduction of the morbidity and mortality in patients with gastric carcinoma.

# THE SURGICAL PROBLEM OF GASTRIC CANCER

WITH SPECIAL REFERENCE TO: (1) THE CLOSED METHOD OF GASTRIC RESECTION. (2) COINCIDENTAL HEPATIC RESECTION AND (3) PRE-OPERATIVE AND POSTOPERATIVE MANAGEMENT

OWEN H. WANGENSTEEN, M.D.

MINNEAPOLIS

Carcinoma of the stomach constitutes a surgical problem of great importance. The main present difficulty still hinges on the matter of making the diagnosis sufficiently early that the benefits of surgery may be extended consistently to a greater number of patients. The nature of the surgical accomplishment in cases of carcinoma of the stomach has improved considerably in recent years.<sup>1</sup> The formidable operative mortality of earlier years largely is disappearing. The experience of this clinic suggests that subtotal resections for cancer of the stomach can be done with a hospital mortality approaching closely that of gastric resection for benign duodenal and gastric ulcers. Improvement in the end results of the surgical management of carcinoma of the stomach is contingent on a larger proportion of patients coming to operation early enough to insure complete eradication of the disease. In a fairly large number of instances still, as will be indicated subsequently, the surgeon finds that his radical resection was essentially a palliative operation, in that the presence of carcinoma cells in the proximal line of resection is not uncommonly observed microscopically. This occurrence suggests that whenever feasible the surgeon must excise a wide margin of apparently normal gastric tissue proximal to the lesion.

## THE DIAGNOSIS

Until a biologic test becomes available to suggest that a patient harbors a malignant growth somewhere in his body, late recognition in many cases undoubtedly will continue. The tragedy of the situation is that a carcinoma per se, certainly in the beginning, gives no symptoms. Only the presence of a complication, ordinarily, informs the patient that things are not as they should be. Ulceration, hemorrhage or obstruction may bring a patient with a gastric cancer to his physician early. More frequently, however, loss of weight and strength and epigastric discomfort suggest the necessity of a visit to the physician.

Alertness on the part of patients to symptoms and wise appraisal of those symptoms by physicians are probably still the most important items in the early detection of gastric cancer. The definite ascertainment of the presence of a gastric lesion must await fluoroscopic and roentgenographic examination. Without question the roentgen rays are the most reliable diagnostic agent. An important

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1. Livingston, E. M., and Pack, G. T.: *End-Results in the Treatment of Gastric Cancer*, New York, Paul B. Hoeber, Inc., 1939. Ogilvie, W. H.: *Cancer of the Stomach*, Surg., Gynec. & Obst. 68:295-305, 1939. Parsons, L., and Welch, C. E.: *The Curability of Carcinoma of the Stomach*, Surgery 6:327-338, 1939. Walters, W.: Gray, H. K., and Priestley, J. T.: *Carcinoma and Other Malignant Lesions of the Stomach*, Philadelphia, W. B. Saunders Company, 1942.

element of the problem is to bring more patients with symptoms for roentgen examination earlier. Fluoroscopic and roentgenographic examinations have their limitations, however, and in certain instances, they fail to reveal a fairly well advanced lesion. Such failures, though infrequent, happen in the experience of the best roentgenologists and serve only to remind one that even this diagnostic agent has its shortcomings. Employment of gastroscopy can make an important contribution to the satisfactory management of such patients—an observation that most clinics have had an opportunity to make.

The roentgenologist has a tremendous responsibility in relaying his findings and interpretations of a *borderline* gastric lesion to the clinician. No one probably appreciates the gravity of that responsibility more than the roentgenologist himself. In the main clinicians are credulous persons and are wont to accept the conclusions of the roentgenologist as those of one who manipulates an infallible divining rod. I have already indicated that the roentgenologist may overlook the presence of a lesion. A more common error and not an infrequent one in diagnosing lesions near or at the pyloric outlet and accompanied by obstruction is confusion of ulcer with carcinoma. What is done to the patient frequently depends very largely on the character of the interpretation of the roentgenologist. I have the feeling that this is a responsibility which should fall more directly on the clinicians and especially the surgeons. In the past, when gastric resection was not as safe an operation as it now is, in the hands of experienced gastric surgeons, the roentgenologist perhaps was correct in having his interpretation carry and express a more conservative attitude in certain cases of dubious nature than he actually felt. Under certain circumstances today, the roentgenologist may feel constrained to continue that tradition. In the interest of the patient (whose interest is always paramount, no matter who the medical attendants may be) the roentgenologist would do well in such situations to suggest that a gastric surgeon may prove a better consultant than time in resolving the true nature of the lesion. Allen and Welch<sup>2</sup> (1941) have indicated that the general conservative attitude toward the problem of gastric ulcer has caused many a patient with a gastric cancer to receive procrastinating treatment for it. In the surgical clinic of the University Hospitals each year my associates and I see several patients with gastric lesions the character of which remains in doubt until well stained microscopic sections of the gastric resection specimen become available for study. In such instances reversal of diagnoses based on examination of the gross specimens, whether expressed by clinician, radiologist, gastroscopist, surgeon at operation or pathologist, has not been infrequent in the experience of this clinic.

Such circumstantial evidence as the closure of an antecedent perforation a few months previously and of the presence of free hydrochloric acid in the gastric juice does not gainsay the presence of carcinoma. During the past year, 2 such patients were seen in the surgical clinic. On the basis of clinical evidence including roentgen examinations, both were believed to have ulcer; both had carcinoma. One was a man of 27 years. The latter patient already has suggestive evidence of recurrence about fifteen months after resection.

The relative frequency with which carcinoma of the stomach has been observed in this clinic in patients under medical treatment for pernicious anemia suggests definitely that all patients with that disease should have a roentgen examination of the stomach three times a year. Even in a clinic in which one professes to scrutinize carefully all patients with pernicious anemia with special reference to

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2. Allen, A. W., and Welch, C. E.: Gastric Ulcer: The Significance of This Diagnosis and Its Relationship to Cancer, *Ann. Surg.* 114:498-501, 1941.

gastric lesions it is surprising how failure to comply rigidly with this self-imposed task results in bringing to the surgeon patients with pernicious anemia who have far advanced carcinomas of the stomach for which only a palliative resection can be done. The frequent occurrence of cancer in atrophic gastric mucous membrane is an item deserving of careful inquiry and study.

#### PREPARATION FOR OPERATION

One of the common causes of mortality, especially in the bad risk patient, has been inadequate preparation. Restoration of a satisfactory hemoglobin value and of water and electrolyte balance is not enough. The adequate preparation of the patient who has lost weight is a fundamental consideration in getting him ready for a formidable operation. A careful inquiry into the extent of the loss of weight, the time over which it was sustained and the character of the food intake in the weeks or months prior to the patient's admission to the hospital is a matter of the greatest moment. In this clinic it has become routine practice to prod the patient's memory repeatedly on this score and to interrogate the relatives closely to get reliable information on the character of the patient's nutrition in the preceding months. The appearance of the patient is not a safe criterion. A person whose food intake has been poor and who has lost considerable weight is not a good operative risk. We have followed the suggestion of Ravdin,<sup>3</sup> who has pointed out the great importance of a high protein and carbohydrate and low fat diet in preparing such patients for operation.

The greatest losses of weight are sustained by patients who have a high grade pyloric obstruction. In such instances, in which the opportunity for absorption of ingested food is very poor or nil, the nutrition of the patient might be described as autocannibalistic, since he has been subsisting on his own food stores. The deposits of glycogen and labile protein are exhausted quickly. Life is sustained largely by deposits of fat (approximately 3,500 calories per pound of human fat) and by a gradual breakdown of body protein. Accompanying the loss in body weight attending such starvation, fat infiltrates the liver, an observation already known to histologists for more than half a century. Only recently have pathologists, biochemists and surgeons concerned themselves over this circumstance. Patients with fatty livers are extremely poor risks for major surgical procedures and tolerate difficult operations poorly. Early in the operation, such patients exhibit great fluctuations in blood pressure, and it is frequently found difficult to sustain a normal blood pressure even when losses of blood are minimal. Yet the feeding of a high protein, high carbohydrate diet to such patients for a period of time—the length depending on the extent of the loss of weight—will succeed almost uniformly in driving fat out of the liver. In the experience of this clinic, patients who have sustained large losses of weight can be brought to tolerate long and trying operative procedures by proper preoperative feeding. Even though the caloric intake of such a high protein and carbohydrate but low fat diet is great, our experience has proved that patients prepared for operation in this manner rarely gain much weight. Such failure to gain weight commensurate with the high caloric intake of such a diet may have to do with the large proportion of protein in the diet and the effect of the specific dynamic action of ingested protein on energy requirements. Moreover, it should not be the surgeon's objective to have the patient gain weight.

3. Ravdin, I. S.: The Protection of the Liver from Injury, *Surgery* 8:204-211, 1940.  
Ravdin, I. S.; Thorogood, E.; Riegel, C.; Peters, R., and Rhoades, J. E.: The Prevention of Liver Damage and the Facilitation of Repair in the Liver by Diet, *J. A. M. A.* 121:322 (Jan. 30) 1943.

Suggestive of the improved condition of the patient's liver attending such feeding are the following facts: There is a gain in strength, so that frequently a patient unable to sit or stand because of loss in weight can be got out of bed. The patient feels subjectively better, and his outlook on the future appears brighter. His complexion improves, and a ruddier color returns to his face.

My associate Dr. Richard L. Varco<sup>4</sup> has compounded two diets which have proved eminently satisfactory. If no pyloric obstruction is present, Varco diet no. I is taken in two hourly feedings through the day. All patients being prepared for extensive operations on the gastrointestinal canal are given Varco diet no. II as an intragastric drip feeding through the night (fig. 2).

Intragastric drip feeding has been employed intermittently in this surgical clinic for years. The Varco no. II feeding mixture has augmented greatly the value of this mode of supplying alimentation. For patients with bleeding ulcer, it has been an agent of the greatest worth, not alone in stopping the bleeding but in preparing the patient for operation. Five or six days after the commencement of massive hemorrhage from a duodenal ulcer a gastric resection can be carried out, apparently with a hazard not out of line with that accepted for standard risk



Fig. 1.—Photograph of a patient receiving intragastric drip feeding of Varco diet no. II. Ingredients of the formula are:

	Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.
Whole eggs—6 .....	....	36.0	36.0
Egg whites—2 .....	....	8.0	....
Skimmed milk powder—113 Gm.....	58.8	40.4	1.2
Lactose—300 Gm. ....	300.0	....	....
Skimmed milk—1,000 Gm.....	50.0	30.0	....
Salt—5 Gm. ....	408.8	114.4	37.2

A patient taking the drip day and night will ordinarily receive 2,500 to 3,500 cc. The caloric content being 1.6 calories per cubic centimeter, the total caloric intake will be 4,000 to 5,600 calories. Gastric retention of course will reduce the caloric intake.

patients. Whenever pyloric obstruction is present, Varco diet no. II is given, 90 cc. per hour both day and night, by the drip method. In patients with pyloric obstruction from a duodenal ulcer, the frequent hypodermic administration of atropine sulfate and sodium phenobarbital diminishes gastric secretion and lessens and frequently abolishes gastric retention. Both diets have a caloric value of 1.6 calories per cubic centimeter. Fifteen hundred cubic centimeters of either the

4. Varco, R. L.: Unpublished data, 1942.

ingested diet (no. I) or the drip diet (no. II) contains approximately 150 Gm. of protein, 400 Gm. of carbohydrate and 30 Gm. of fat (detailed analysis in legend for figure 2). Skim milk (casein) constitutes the chief source of protein in the diet.

Employment of beef serum as part of the diluent in the drip feeding mixture (Varco diet no. II) probably will enhance the value of the diet in the regeneration of plasma protein; addition of the pressed juice of raw liver may prove valuable also. Such a diet then would serve two purposes: (1) rid the liver of fat deposits incident to starvation and (2) help rebuild plasma protein and replenish the depleted stores of deposit protein. The splendid paper by Madden and Whipple<sup>5</sup> (1940) on the latter phase of the problem should be studied carefully by all surgeons interested in extending the benefits of surgery to poor risk patients without increasing materially the hazards of such operations. Beef serum and liver are far superior to casein in bringing about regeneration of plasma protein.

#### THE PROBLEM OF FEEDING PATIENTS WITH HIGH GRADE OR ABSOLUTE PYLORIC OBSTRUCTION

When pyloric obstruction is absolute or nearly so, intravenous feeding must be relied on solely. At the outset it is to be conceded freely that intravenous feeding



Fig. 2.—Photograph of a patient of 82 years with pyloric obstruction from a malignant gastric tumor. The photograph was taken about a week after operation; the left subcostal incision can be seen. Vomiting over a period of months had caused her to lose 60 pounds (27 Kg.) (from 165 to 105 pounds [75 to 48 Kg.]), approximately 37 per cent of her weight. Despite a fairly high grade pyloric obstruction, she took the constant intragastric drip feedings well. After twenty days of preparation, an 80 per cent gastric resection was done, and the patient was dismissed sixteen days after operation. Before operation she could neither sit up nor stand. She has been in the outpatient clinic since operation and reports that she is active again and has regained considerable weight. Patients with larger losses of weight have withstood operation in this clinic; this patient, however, presented the greatest percentile loss of weight, after which resection has been done successfully for gastric cancer.

is a poor substitute for a high carbohydrate and high protein diet, in which the protein employed has good capacity to induce the regeneration of plasma protein. Nevertheless, by a combination of plasma and amino acids and a fairly liberal quantity of dextrose solution in 10 to 20 per cent concentration, nitrogen and caloric equilibrium can be approximated. It is our experience that plasma is more likely to be successful in increasing the plasma proteins than are amino acids. As a matter of fact, only one stage operations for pyloric obstruction of benign or malignant origin have been done in this hospital over a period of more than three years. The

5. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization, *Physiol. Rev.* 20:194-217, 1940.



experience up to October 1940 was recorded previously.<sup>6</sup> My associates and I have now carried through a large number of one stage gastric resections for pyloric obstruction of benign as well as malignant origin without mortality. The greater number of the patients have been prepared by the intragastric drip feeding. Nevertheless, there are a few patients whose pyloric obstruction has been absolute or nearly so who have been prepared by intravenous feeding alone, in the manner described.

#### WATER, ELECTROLYTE AND VITAMIN REQUIREMENTS

The teachings of Coller and his associates<sup>7</sup> have made all surgeons more thoughtful on this score. My practices<sup>8</sup> in this regard have been described previously and need not be repeated here. Inasmuch, however, as the surgery of gastric cancer concerns patients in the upper age brackets largely, one must exercise great care not to give them too much salt or too much water—and the fluid, no matter how it is given, must be given *slowly*. Most of these patients have poor cardiac reserve and to be indifferent to matters of increasing the blood volume invites cardiac embarrassment, pulmonary edema and pneumonia.

#### THE AGE FACTOR

At one time, I was disposed to account for the disparities in mortality of gastric resection for benign and for malignant lesions of the stomach, largely on the basis of differences in age.<sup>6</sup> The majority of patients having gastric resection for ulcer are under 50. Approximately 50 per cent of patients having resection for cancer are over 60, and 20 per cent are over 70. Some are over 80. Whereas the mortality of gastric resection for benign lesions has been approximately 2 to 3 per cent in this clinic, the mortality of resection for gastric cancer for the same period of years has been significantly greater, hovering about 10 to 12 per cent. However, in the past year (Sept. 1, 1941 to Sept. 1, 1942), the differences in mortality of resection for benign and for malignant gastric lesions have largely been erased, as will be indicated subsequently. The chief factor in the reduction of the mortality has been better and more careful preoperative preparation, as has been outlined.

Obviously the surgeon accepts more risks in operating on an elder group of patients, but the experience of this clinic suggests that careful preoperative preparation and judicious management of the patient during and after operation have done away largely with the special hazards incident to age. In this series of resections, 65 per cent of the patients were 60 years of age or more; 22.5 per cent were 70 or more.

#### THE OPERATION

An operation should be made to simulate physiologic sleep, during which the disease process is spirited away. This objective never can be attained, yet with wise planning and deliberate thought beforehand much can be done to avoid making the sleep of operation fitful and disturbed; fluctuations in the level of anesthesia and in the blood pressure are to be avoided. Tissues must be handled

6. Wangenstein, O. H.: Aseptic Resections in the Gastro-Intestinal Tract, with Special Reference to Resection of the Stomach and Colon, Surg., Gynec. & Obst. **72**:257-281, 1941.

7. Coller, F. A., and Maddock, W. G.: Water and Electrolyte Balance, Surg., Gynec. & Obst. **70**:340-354, 1940.

8. Wangenstein, O. H.: (a) The Controlled Administration of Fluid to Surgical Patients, Including Description of Gravimetric Methods of Determining Status of Hydration and Blood Loss During Operation, Minnesota Med. **25**:783-789, 1942; (b) Intestinal Obstructions: A Physiological and Clinical Consideration with Emphasis on Therapy, Including Description of Operative Procedures, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1942; (c) footnote 6.

gently, and loss of blood must be minimal. Use of dry sponges and the weighing scale during operation <sup>9a</sup> to ascertain loss of blood will make the surgeon and his associates "blood loss minded," a very important contribution to simulation of physiologic sleep during operative procedures, especially for substandard risk patients.

One unaccustomed to consider operation in this light is prone to believe that operation is an ordeal which should be got through quickly and that the time element is the all-important consideration in the success or failure of an operation. Surgeons who hold to this view frequently cause their patients to have a fitful operative sleep, wholly unaware that their own hurry is largely responsible for the uneven course manifested by the patients during operation. They conclude quite naturally, therefore, that if an operation of an hour or two in their hands constitutes a major ordeal for the patient, longer operations are obviously out of the question. These same surgeons are skeptical and manifest signs of unmistakable incredulity when informed that a patient of 80 years or more can be maintained through a long and arduous operative ordeal, when well prepared for operation, without exhibiting quickening of the pulse or decline of blood pressure. To be sure protects the patient's interests far better than to be swift. Nothing should be left to chance. The operation should be done in such a manner that the patient has to contend only with it not with the complications incident to hurry.

Obviously it takes an organized team of anesthetists, nurses and surgeons working together harmoniously with precise coordination to make a long and difficult operative procedure simulate physiologic sleep. A high level of concentration and alertness must be maintained for the task at hand by all participants. The anesthetist must not go to sleep with his patient. And the surgeon must cultivate the attitude of trying to perform every phase of the operation to his own complete satisfaction. The patient's welfare is the paramount consideration; the matter of whether a difficult resection should be undertaken or not should not be made contingent on whether the surgeon has allotted himself adequate time in which to complete it. The surgeon in justice to his high calling and to his patient should put aside every other concern and discharge to the best of his ability the responsibility he has undertaken—an instruction more easily given to others than followed consistently by oneself. The great importance of the surgeon's resigning himself completely to the interests of the patient being operated on long since convinced me that afternoon operating schedules more easily permit the surgeon to follow this self-imposed obligation of putting aside every other consideration in order that he may do his best work and serve his patient best. All need for hurry to meet appointments and fulfil luncheon engagements is done away with. Such a program impels the surgeon to appear a less social being than his own instincts suggest. This is only another concession which he learns to support without complaint in the interests of his patient and his calling. What right has the surgeon to permit any commitments of the day to conflict with concern for the patient during his trial of suspended animation, since it is his interests that the surgeon professes to regard as dominant?

For a period of more than four years, all anastomoses in the gastrointestinal canal in this clinic have been made by the closed, or aseptic, method. The closed method of gastric resection which I described in 1940<sup>9</sup> and again in (1941)<sup>6</sup> has

9. Wangenstein, O. H.: Aseptic Gastric Resection: I. A Method of Aseptic Anastomosis Adaptable to Any Segment of the Alimentary Canal (Esophagus, Stomach, Small or Large Intestine); II. Including Preliminary Description of Subtotal Excision of the Acid Secreting Area for Ulcer, Surg., Gynec. & Obst. 70:58-70, 1940.

been continued with no important changes in the technic. The latter paper describes in detail all the essentials of the procedure, of which only a tabular outline will be given here. Holman<sup>10</sup> and Babcock<sup>11</sup> (1942) more recently also have adopted the closed method of gastric resection.

1. The patient goes to the operating room with an indwelling duodenal tube (nine hole tube) in place, great care having been observed to have the stomach completely empty; suction is continued throughout the period of the operation.

2. The anesthetic agent is intratracheally administered cyclopropane. During the past year spinal anesthesia (not continuous) has been employed fairly regularly as an adjuvant measure to augment relaxation during the early part of the operative procedure.

3. Exposure is obtained through a long left subcostal incision (fig. 3). Gastric resection carried out through this incision, save for delivery of a jejunal coil of intestine with which to establish the anastomosis, is entirely a supracolic operation. Almost throughout the length of the procedure, therefore, the small intestines need not be exposed nor visualized (see item 5).

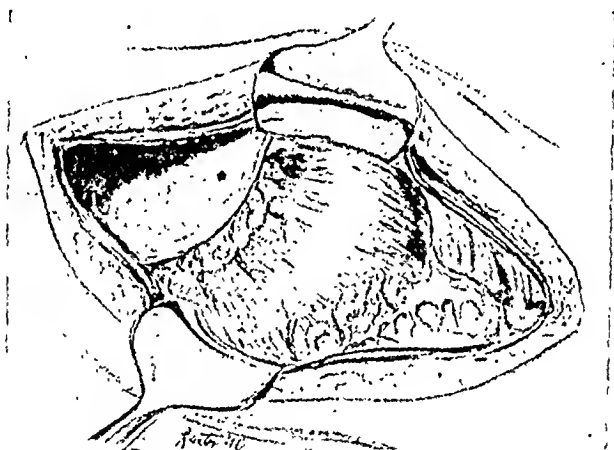


Fig. 3.—The exposure through a left subcostal incision. Ready access is had to the fundic portion of the stomach; the duodenum may be dealt with readily through the same incision. This incision for gastric resection has many advantages. An important one is that it is entirely a supracolic exposure, eliminating the necessity for packing away the small intestine. (Reproduced from Wangenstein,<sup>6</sup> by permission of *Surgery, Gynecology and Obstetrics*.)

4. The anesthetist not objecting, the patient is maintained in slight Trendelenburg position throughout the operation, with the feet 15 to 20 cm. higher than the heart level. An intravenous needle or cannula is placed regularly in one of the ankle veins before the operation is begun, and a slow trickle of saline solution is maintained at the outset to keep the needle open.

5. Only dry sponges are employed, save where a retentive pack may come in contact with the small intestine. Inasmuch as the complete dissection in the ordinary gastric resection as carried out in this clinic through a long left subcostal incision is almost entirely a supracolic operation, save for anchoring the final stoma beneath the transverse mesocolon, there is rarely need for employment of any moist saline packs. In all infracolic operations, restraint of movement of the small intestine

10. Holman, E.: Aseptic Resection of Stomach for Carcinoma and Ulcer, *Surg., Gynec. & Obst.* **74**:146-152, 1942.

11. Babcock, W. W.: Aseptic Gastrointestinal Anastomosis: A One Clamp Method of Universal Application, *Surg., Gynec. & Obst.* **75**:485-498, 1942.

must be attained by wet packs. In such instances, these packs are counted but not weighed. The nonsterile room nurse at the foot of the table weighs the retrieved sponges periodically through the operation; this practice has been important in aiding the surgeon to gage loss of blood. Further, it has served to make him "blood loss conscious." Surgeons who initially caused the loss of 400 to 600 cc. of blood during gastric resection learn soon to do the same operation in uncomplicated cases frequently with loss of only 150 to 250 cc. In a difficult case, with extragastric extensions, a far larger loss of blood must be produced occasionally to determine operability alone. Early in the operative procedure, the infusion of plasma is begun. Only enough plasma should be given to cover the loss of blood adequately. Blood is not given, save in the occasional difficult case in which the loss of blood is large.

6. Operability is a relative term. Unless unmistakable signs of inoperability are present, operation is undertaken regularly. No patient has been refused operation in this clinic during the past few years because of age alone. A large cul-de-sac mass or large ascites with evidence of peritoneal carcinosis and jaundice contraindicates operation. Of the cases in which exploration is done, resection is still performed in the majority. In the report of 1941,<sup>6</sup> the resection rate in the cases in which exploration was done was 88.5 per cent; obviously, a number of the operations were palliative resections. During the past year, the resection rate in the cases in which exploration was done was 88.2 per cent; and obviously this figure includes only cases of patients submitted to operation. The patients whose condition is frankly inoperable are turned away in the medical outpatient clinic. Age, anemia, obstruction and loss of weight do not militate against operation.

When exploration is undertaken, only the finding of unexpected peritoneal carcinosis or evidence of widespread and intimate adherence of the growth to the diaphragm and pancreas, especially when accompanied by the presence of large para-aortic nodes, suggests that operation be limited to exploration. A few hepatic metastases do not constitute contraindication to resection, save when total gastrectomy would be necessary. In the presence of direct extension into the liver, simultaneous excision of a part of the lobe involved is undertaken. Four hepatic resections were done incidental to resection for gastric cancer during the past year. In one of these, practically all of the left lobe of the liver was excised. Adherence of the tumor to the pancreas, the transverse mesocolon or the colon does not contraindicate resection. Simultaneous resection of the colon with the stomach was done three times for gastric cancer during the past year. Occasionally a stone-containing gallbladder or stones encountered in the common duct have been excised too before the abdomen is closed.

7. Complete excision of the omentum up to the gastrosplenic omentum is done regularly to remove the lymph nodes between the stomach and the colon. Great care is observed to remove as much of the gastrohepatic omentum as is possible and also to remove all visible or palpable lymph nodes from within it. Recently, in the case of a man aged 38 with pernicious anemia of seven years' duration, presenting two large malignant polyps in the stomach, one of which was near the esophago-gastric juncture, a group of about a dozen large para-aortic lymph nodes was found. These nodes extended as a chain of large isolated nodules, one node on either side of the aorta, from the celiac axis to the inferior mesenteric artery. By elevating and retracting the pancreas both upward and downward, it was possible to remove the nodes between the celiac axis and the superior mesenteric vessels. The other para-aortic nodes beneath the transverse mesocolon were removed without difficulty.

Lymph fistula did not follow, and the patient was dismissed from the hospital ten days after a 95 per cent gastric resection.

Such a procedure probably will prove to be only a gesture. Yet, if the local lesion is removed completely, deposits of malignant cells may be restrained within the confines of lymph nodes for a long time. The observation of an instance in which a somewhat similar dissection and removal of large lymph nodes from the gastrohepatic omentum together with the local lesion in the stomach was followed by a period of freedom from symptoms of more than thirty months suggests that such attempts at palliation may have some merit. The patient just referred to died thirty-three months after gastric resection. A solitary large node near the porta

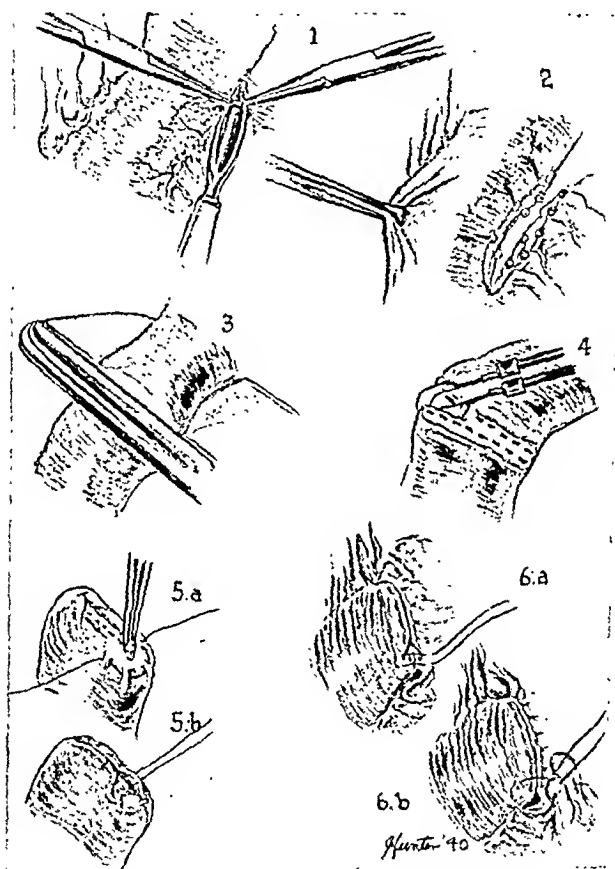


Fig. 4.—The steps in dissection and closure of the duodenum. Employment of the "half purse strings" at the ends combined with a few Halsted mattress sutures constitutes an eminently satisfactory method of closing the duodenum. The reattachment of the pancreatic capsule (6a and b) affords assurance that a secure closure has been obtained. The "half purse strings" shown in 5a insure good duodenal inversion with a few extra interrupted Halsted mattress sutures in the first row. Two rows of sutures are placed usually. If the duodenal mobilization is adequate, both rows may be placed in the duodenal wall. Many times it is necessary, however, to place the second row in the pancreatic capsule as shown here (6a and b). (Reproduced from Wangenstein, footnotes 6 and 12, by permission of *Surgery, Gynecology and Obstetrics*.)

hepatitis had occluded the common bile duct and produced jaundice. There were no other residuals.

8. The duodenum is divided after application of the Petz suturing apparatus, and inversion is achieved with two rows of interrupted silk sutures.

The two half purse strings in the first row, which I described in 1940,<sup>12</sup> have proved an eminently satisfactory means of achieving inversion. Obviously, the duodenal mobilization to permit inversion must be adequate. Drainage need not be employed, and no duodenal fistulas following gastric resection have been observed in this clinic in several years. The importance of good duodenal inversion contributes much to the safety of gastric resection.

9. The entire lesser curvature of the stomach must be excised (fig. 6). Failure to remove it frequently leaves residual cancer cells in the proximal line of resection and makes an otherwise satisfactory operation but a palliative procedure. The left subcostal incision facilitates access to the esophagus and the fundus of the

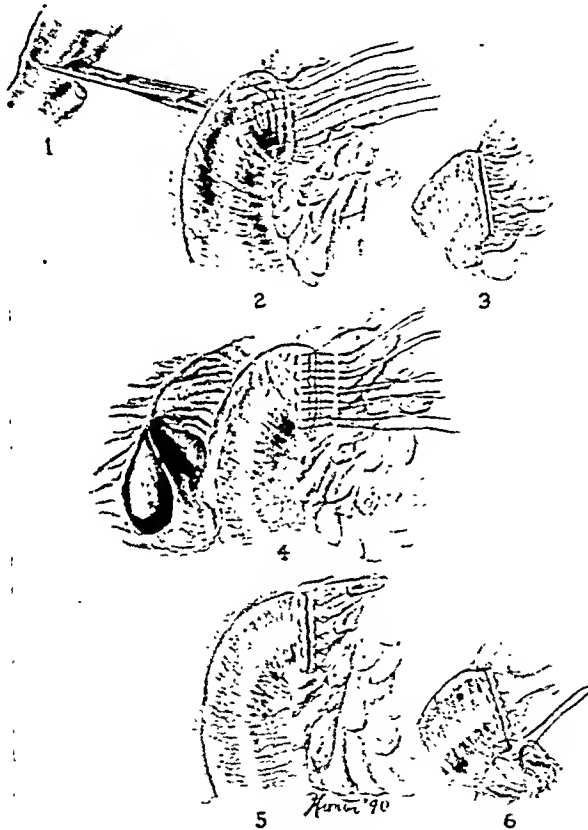


Fig. 5.—The steps employed in securing satisfactory closure of the duodenum in the presence of duodenal invasion. This type of duodenal closure need not be employed frequently with gastric cancer. The surgeon must use it frequently for patients with massive hemorrhage from a duodenal ulcer and for nonbleeding patients who have a posterior wall duodenal perforation. Division of the avascular ligament of the duodenum as shown in 4, brings the duodenum nearer the midline and obviates tension. This separation also permits visualization of the common bile duct and affords the surgeon reliable information concerning the extent to which he may mobilize the duodenum. (Reproduced from Wangenstein,<sup>6</sup> by permission of *Surgery, Gynecology and Obstetrics*.)

stomach. When the entire lesser curvature is excised, the residual blood supply of the stomach comes from two or three gastric vessels from the splenic artery. Great care must be observed, therefore, not to injure that vessel (fig. 14).

12. Wangenstein, O. H.: The Problem of Surgical Arrest of Massive Hemorrhage in Duodenal Ulcer, *Surgery* 8:275-288, 1940.

10. The extent of the excision on the greater curvature depends largely on the location of the lesion (figs. 7, 9, 10, 11 and 13). Even for a neoplasm located definitely (apparently) in the antrum, a 75 to 80 per cent gastric resection should always be done as a minimum. In this clinic the usual extent of the excision for gastric cancer is an 80 to 90 per cent resection. During the past year, only 2 total resections were done, but there were 15 in which the extent of the excision was 90 per cent or more (table 3).

I employ the Hofmeister procedure regularly in effecting the gastrojejunal anastomosis. Inversion of the upper end of the lesser curvature in the gastric wall (fig. 7 *D*) simplifies the surgical problem. The extent of a gastric resection as carried out in this clinic is varied largely by the elevation of the point of resection

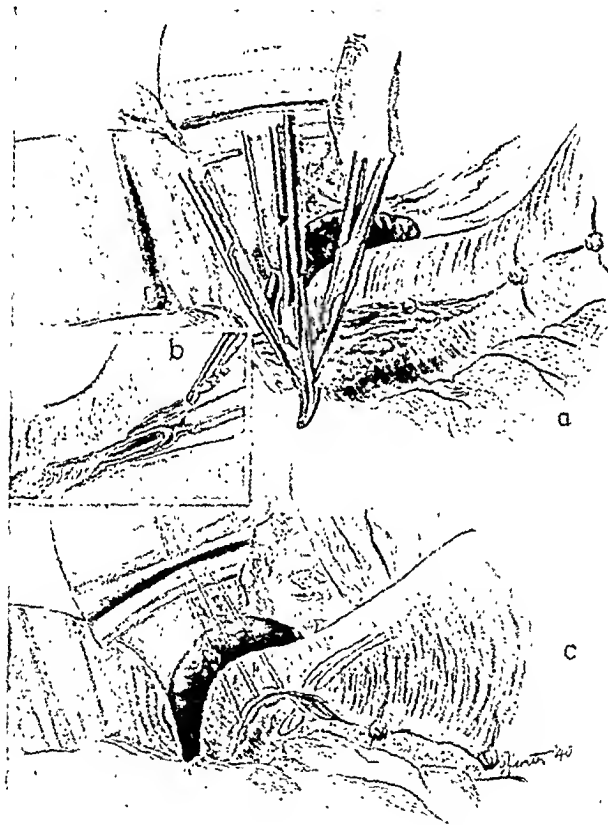


Fig. 6.—Preparation of the lesser curvature. *a*, ligature of the left gastric artery. *b*, division of the peritoneal folds (anterior and posterior) to the esophagus. *c*, closure of the peritoneal defect at the upper end of the lesser curvature by interrupted silk sutures shown here has been abandoned. These sutures are placed now only after amputation of the stomach as shown in figure 7 *C*. (Reproduced from Wangenstein,<sup>6</sup> by permission of *Surgery, Gynecology and Obstetrics*.)

of the greater curvature (figs. 7 and 14). In all resections below 95 per cent, there is invariably enough remaining fundus to permit good closure of the upper end of the lesser curvature. In excisions of more than 95 per cent, burying the upper end of the divided lesser curvature in the residual gastric fundus becomes impractical. Under such circumstances, after placement of the Halsted mattress sutures of fine silk (fig. 7 *D*) remnants of the gastrohepatic omentum, the pancreatic capsule at this level or the proximal jejunal loop may be employed to reinforce the suture line. I have on a few occasions, when the lower end of the right border of the esophagus was involved, removed a strip of it, together with the

entire lesser curvature of the stomach; in these instances, especially if the gastric resection is large, it almost invariably becomes necessary to resuture the esophagus, without the advantage of burying it in the gastric fundus. The repaired esophagus in such instances looks not unlike a gooseneck 5 to 8 cm. in length. Obviously, a total gastrectomy would be a simpler procedure in some such cases. Yet, in my hands at least, the procedure described herein is a safer procedure than total gastrectomy.

11. A closed anastomosis 6 cm. in length as depicted in the accompanying diagrams is made with two rows of sutures; the outer row is constituted by interrupted Halsted mattress sutures of fine silk and the inner row by a running suture of fine catgut. The anastomosis is made at the ligament of Treitz; in achlorhydric stomachs, the matter of the level of the anastomosis is not so important.

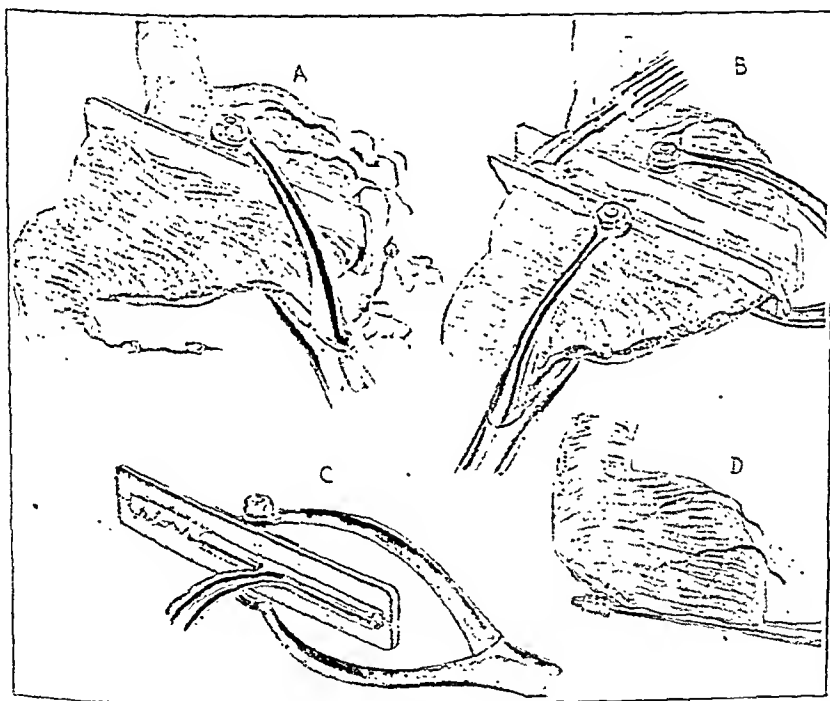


Fig. 7.—*A*, placement of the large adjustable clamp on the stomach. Note its angle, permitting division of the lesser curvature at the esophagus. *B*, after placement of the upper clamp, the burrs above and below the blades are loosened with the wrench shown in figure 8; the handle is then swung out in the axis of the blades, the lower clamp with the resection ledge is applied and the cautery amputates the stomach. The amputation is done along the margin of the resection ledge. *C*, a 6 cm. clamp grasps the lower end of the divided stomach, at the site chosen for the anastomosis. The upper end is whipped over with a running suture of fine catgut. A large roller-skate type of key (fig. 8) is employed to unlock the handles, permitting removal of the large adjustable clamp. The aseptic anastomosis clamp, shown in *D*, is then applied. The cautery (not shown here) is used again to sever the gastric tissue held in the grasp of the 6 cm. clamp. Then, finally, the coagulating current of a surgical diathermy apparatus (Bovie unit with dials set at 70) is applied for three seconds. The final situation is shown in *D*. No instance of postoperative gastric hemorrhage has been observed in more than 200 consecutive gastric resections in which the closed method of anastomosis employing the Hofmeister maneuver shown in figures 9 and 10 was used.

In resections for ulcer, the site of the anastomosis is extremely important. Jejunal anastomosis with a long proximal loop in resections for duodenal ulcer predisposes



to stomal ulcer even though the gastric resection is extensive (1942).<sup>13</sup> Entero-anastomosis is performed in this clinic only when total gastrectomy is done. A small amount of sulfathiazole is implanted about the anastomosis, 1 or 2 Gm., of which the larger amount is placed above the transverse mesocolon. Sulfathiazole does cause adhesions, and only a tiny film of the powder should be rubbed over the suture line, below the transverse mesocolon. A total implantation of approximately 3 Gm. suffices for the whole operative field, including the abdominal wall. No additional sulfonamide compound is given ordinarily by any route for forty-eight hours (see item 5, in the section on postoperative treatment).

The importance of inverting a minimum of tissue cannot be stressed too much<sup>14</sup> (fig. 12). In a group of more than 200 consecutive gastric resections performed in this clinic for malignant tumor and for ulcer, not a single instance of post-operative gastric retention has been observed. These observations suggest definitely that the surgeon is responsible for postoperative obstruction at the efferent gastric outlet.

12. The indwelling gastric tube (nine hole) is inserted into the proximal duodenal loop. Since the anastomosis is made regularly at the ligament of Treitz

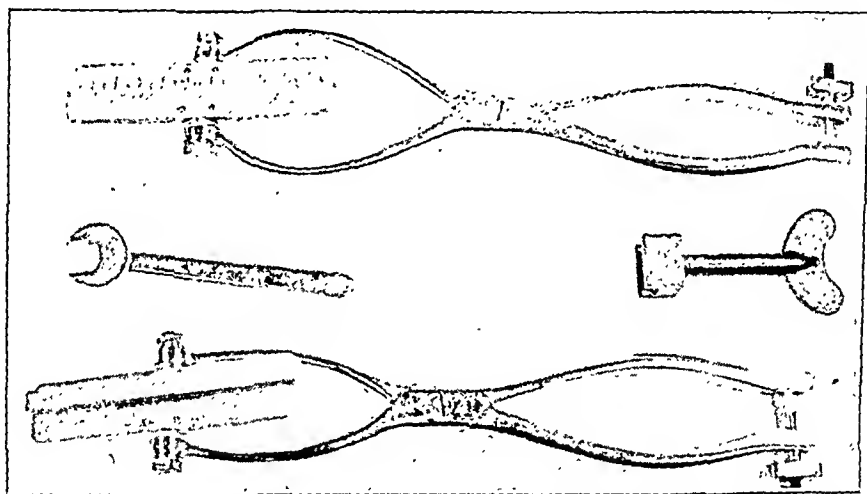


Fig. 8.—Gastric clamps for the closed gastric resection. The clamp above the wrench is applied first. By loosening the burrs above and beneath the blade, the handles may be rotated into the most convenient position. The clamp below the wrench presents a resection ledge. This clamp comes away with the segment of the stomach to be removed. Figure 7 indicates how the clamps are used in the closed gastric resection. The roller-skate type of key shown on the right is used to loosen and tighten the clamp which compresses the blades. These adjustable clamps, as well as the anastomosis clamps shown in figures 9 and 10, are made by V. Mueller & Co., of Chicago.

in partial gastric resection, the proximal duodenojejunal loop becomes merely the duodenal loop (fig. 11).

13. Interrupted fine silk sutures are used throughout the operative procedure, save in the inner row of the anastomosis.

13. Wangenstein, O. H.: *The Surgical Management of Ulcer: A Chemical Problem, Including Description of How the Secretion Factor Influences the Success of Anastomotic Procedures*, Proc. Interst. Postgrad. M. A. North America, to be published.

14. Wangenstein, O. H.: (a) *The Cause and Prevention of Stomal Obstruction in Gastrojejunal Anastomoses (Gastric Resection and Gastrojejunostomy)*, in *Medico-Surgical Tributes to Harold Brunn*, Berkeley, Calif., University of California Press, 1942, pp. 551-562; (b) *Some of the Advantages of Closed Anastomosis in Gastrointestinal Resections*, Proc. Interst. Postgrad. M. A. North America (1941). 1942. pp. 161-166.

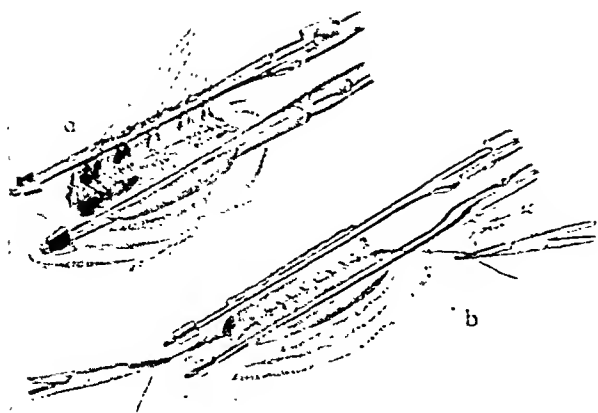


Fig. 9.—The posterior portion of the gastrojejunal anastomosis. In *a* is shown placement of the first posterior row of interrupted Halsted mattress sutures. These sutures are to be placed at a distance of not more than 0.75 cm. away from the clamp. Note position of the clamps, rotated to permit easy placement of the sutures. Five or six sutures are placed before any are tied. Additional sutures are then placed between, making a total of ten to twelve. As each is tied, the assistant (second) who holds the clamps rotates them inward to afford maximal approximation at the site of the tie. In *b* is shown the second posterior suture (running chromic catgut no. 000). The portion of the jejunum above the clamp is not yet removed. (Reproduced from Wangenstein,<sup>6</sup> by permission of *Surgery, Gynecology and Obstetrics*.)

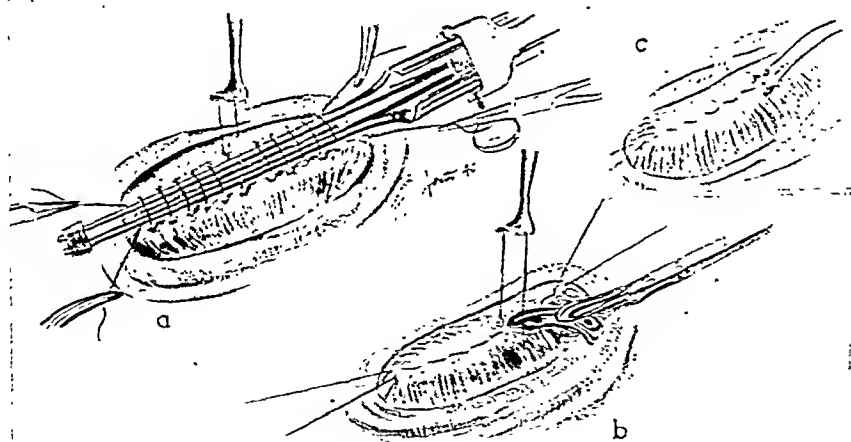


Fig. 10.—The anterior portion of the anastomosis. In *a*, the jejunum above the clamp (fig. 9) has been cut away with the cautery—not directly on the clamp but about 1 mm. above it. The single ferrules shown in figure 9 have been removed, the handles of the clamps have been rotated, the double ferrule has been applied, engaging the tips of both clamps, and the approximation device over the handles is in place. In *b*, the running catgut suture shown in *a* is pulled out after removal of the clamps. Elevation of the midportion of the suture on an eyelid retractor permits aspiration of the residual gastric pouch with a sucker, after which the catheter is pulled out with an alligator type of forceps. The catheter is placed carefully into the proximal duodenal loop of the anastomosis. In *c*, after the catheter is in place, the anterior catgut suture at each end is tied to the posterior running catgut suture. Before these ends are tied, a fine silk suture is placed at each end, to prevent buckling or a "purse string effect" when the anterior and posterior sutures are tied. (Reproduced from Wangenstein,<sup>6</sup> by permission of *Surgery, Gynecology and Obstetrics*.)

## POSTOPERATIVE TREATMENT

The essentials of sound postoperative care have been outlined elsewhere<sup>8</sup> and will be presented here only in outline form:

1. During operation the anesthetist keeps the patient's trachea dry by frequent aspiration through the intratracheal tube. If the patient's bronchi seem wet on completion of the operation, bronchoscopy is done—an infrequent occurrence in our experience.

2. The patient is transported on his side in slight Trendelenburg position on the litter to his room.

3. The application of suction to the intragastric duodenal tube is commenced again and continued without interruption for seventy-two to eighty hours. The continuous use of suction during the early recovery period prevents distention; in consequence, the patient needs less sedation for pain than he does with a

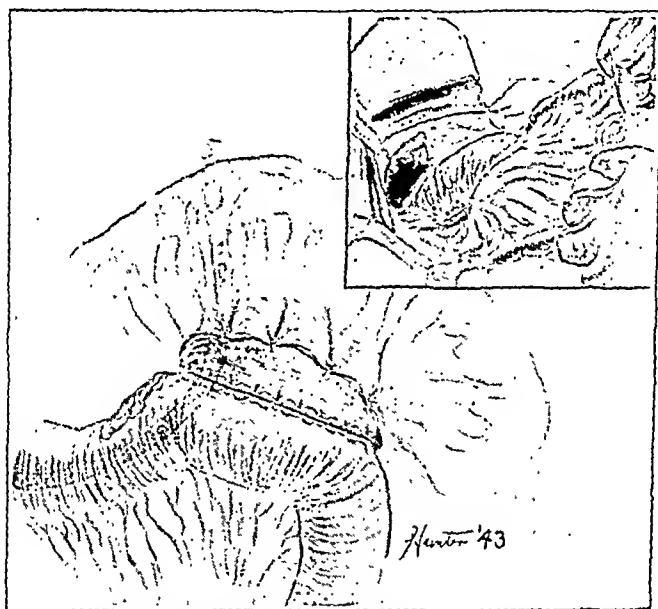


Fig. 11.—The completed anastomosis. A row of interrupted Halsted mattress sutures of fine silk (Deknata D, 2 pound [0.9 Kg.] test strength) has been placed over the catgut shown in figure 10. Care has been observed to anchor the slit in the transverse mesocolon to the gastric wall 1 to 2 cm. above the suture line. The previous attachment of the ligament of Treitz to the beginning of the jejunum (dissected free) is shown just proximal to the anastomosis. The catheter, with holes for suction, both in the duodenal loop and the residual gastric pouch, is shown in situ. The insert shows the residual gastric pouch seen from above the transverse mesocolon. There apparently being no necessity for a tube in the efferent jejunal loop, use of the forked tube has been abandoned.

distended bowel. The patient is allowed water to drink as soon as he awakens after operation. For purposes of avoiding too frequent changing of the suction bottles, the fluid intake is limited to 2 liters per day. Very few patients wish to exceed this amount, with a satisfactory paraoral intake of fluid. The hypodermic administration of small doses of sodium phenobarbital three or four times a day makes the patient less apprehensive; in consequence, he complains less about the irritation of the tube in the throat.

4. On the patient's arrival in his room, the foot of his bed is elevated on the shock frame shown in figure 16. It is kept on the top rung until he is awake.

This supports the blood pressure and permits gravitation of any tracheal secretions into the patient's nose or mouth, from which they may be aspirated readily. All patients, no matter what their financial status may be, are provided with special nursing care during the early convalescent period. The nurse aspirates the mouth, nose and pharynx frequently during the early hours of convalescence to remove mucus. With a well sustained blood pressure and with recovery of the patient's reflexes, the foot of the bed is lowered gradually down to the last rung of the shock frame—usually six to eight hours after operation. However, as long as the indwelling gastric suction tube is in place, the foot of the bed remains elevated on the lowest rung of the shock frame. In this position, the patient's feet are constantly higher than the heart level, insuring a low venous pressure in the leg veins, precluding at the same time slowing and stasis of the venous current. As

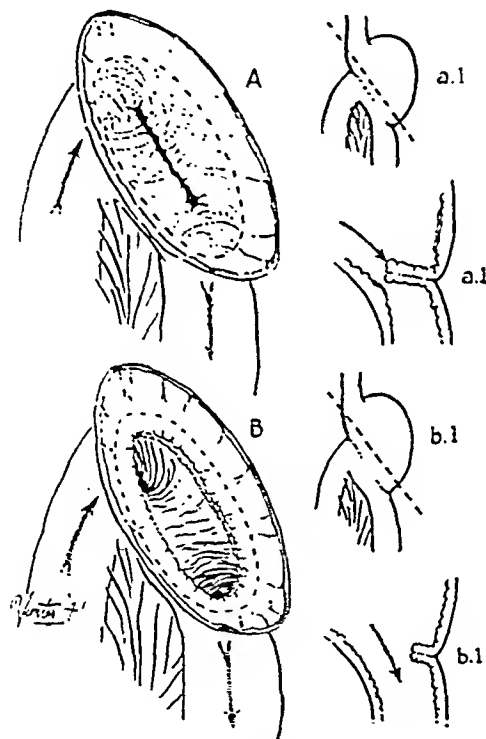


Fig. 12.—Mechanism of obstruction at the efferent outlet after gastrojejunal anastomoses. *A*, inversion of too much tissue creates a flap, which obstructs at the efferent outlet. Obstruction at the afferent inlet through such an agency is distinctly unusual. *B*, the gastrojejunal stoma after incorrect and correct suture. In *a 1*, is shown an oversuturing (incorrect) with a narrow stomal slit and an obstructing flap at efferent outlet; in *b 1*, a wide stomal slit with large patulous stomas at the inlet and outlet (correct), after inversion of 0.5 cm. of the adjacent gastric and jejunal walls in the anastomosis. A large number of consecutive gastric resections for ulcer and carcinoma (more than 200) have now been done by the closed method, in which great care has been taken not to invert more than 0.75 cm. of the gastric and jejunal walls in the anastomosis. No instance of gastric retention has been observed in the group after withdrawal of the inlying duodenal tube seventy-two hours after operation (fig. 11). (Reproduced from Wangenstein, footnotes 8 *a* and 14 *a*, by permission of *Surgery, Gynecology and Obstetrics*.)

soon as the patient recovers from the anesthetic and is well oriented, the importance of moving his toes is enjoined on him. By nurses and surgical house officers alike, the patient is urged a dozen times or more a day to "move his toes incessantly.

when awake—a thousand times a day!" The oxygen tent is employed rarely and only on positive indication, such as dyspnea or cyanosis. In the main, if complications can be avoided, the administration of oxygen practically can be dispensed with after resections in the gastrointestinal canal. Good nursing care contributes far more to the patient's safety and comfort.

Fowler's position is not employed. Late in convalescence (about the eighth day), the patient may sit up against a back rest to eat, but as long as he remains in bed he is asked to lie flat with the knees straight, no pillow being permitted beneath the knees. During the period when the patient is confined to bed,

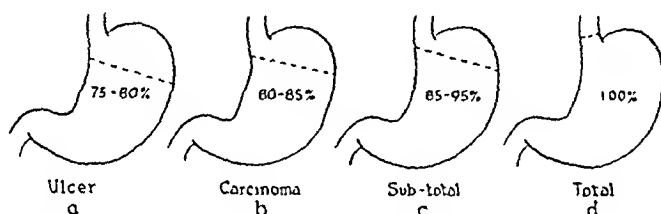


Fig. 13.—Usual extent of excision of gastric tissue in this clinic. In *a* is shown the most frequent site of amputation for both ulcer and cancer. Great care is observed in resections for cancer to remove the entire lesser curvature. For high lesions, the operations in *b* and *c* are done. The only manner in which they differ from that shown in *a* is in the extent of excision on the greater curvature of the stomach. In resections of less than 95 per cent, it is not difficult ordinarily to bury the esophagus at the lesser curvature in the fundus of the stomach as shown in figure 7 *C*. In resections of more than 95 per cent, it is frequently impossible to accomplish this. It then becomes necessary to cover the right border of the esophagus with the residual adjacent edges of the gastrohepatic omentum at that level. In *d* is represented total gastrectomy. (Reproduced from Wangenstein,<sup>6</sup> by permission of *Surgery, Gynecology and Obstetrics*.)

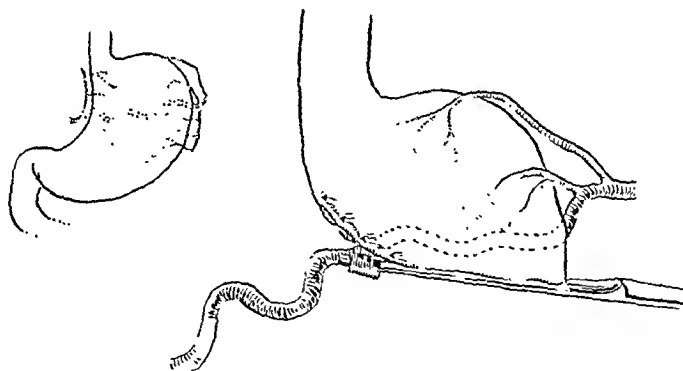


Fig. 14.—The residual gastric pouch in the 75 to 80 per cent resection. It is to be noted that the residual gastric pouch gets its entire blood supply from two short gastric vessels, branches of the splenic artery. Ordinarily, in gastric resections in excess of 85 per cent, only one short gastric artery is left. It is obvious that caution must be observed not to injure the splenic artery. If the splenic artery or the remaining short gastric arteries are injured, total gastrectomy must be done. The large adjustable gastric clamps shown in figures 7 and 8 have a blade which may be rotated on the handles. These clamps were devised for use with the left subcostal incision to permit maneuverability, at the same time assuring maximal protection to the remaining blood vessels. The insert shows the normal blood supply of the upper portion of the stomach. The left and right gastric arteries and the gastroepiploic artery are interrupted completely in the operation as I perform it.

he is turned from side to side frequently (every two hours day and night, unless asleep). These strictures have, I believe, a telling effect. Instances of death from

pulmonary embolus alone have not been observed in the gastrointestinal surgical service in this clinic over a period of several years. Urging constant movement of the toes on the patient during waking hours has another advantageous effect: When the patient gets up nine days after operation he finds himself usually strong enough to stand and frequently able to walk.

5. A large number of patients with carcinoma of the stomach are old and have impaired cardiac reserve. It is important, therefore, *not to overhydrate* or *overchlorinate* the patient with sodium chloride solution. Unless unusual quan-

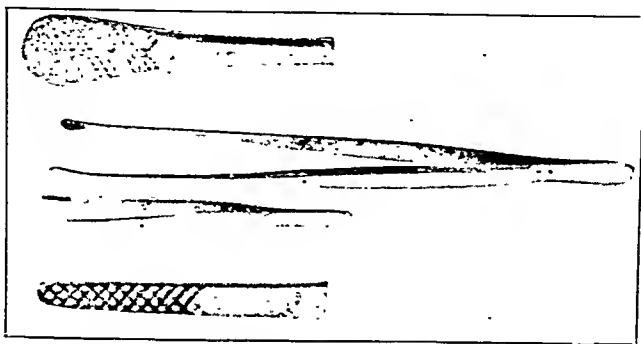


Fig. 15.—Special tissue forceps for use in grasping silk ligatures. The larger instrument is a nicely balanced instrument with a gentle spring, 24 cm. in length and weighing approximately 60 Gm.; the smaller instrument is 12 cm. in length and weighs about 20 Gm. Note the crisscross striations. Such cross hatchings make it feasible to catch fine silk sutures regularly. Slipping of fine sutures when grasped with tissue forceps having the ordinary transverse striations is a matter of common experience. (Available through V. Mueller & Co., Chicago.)

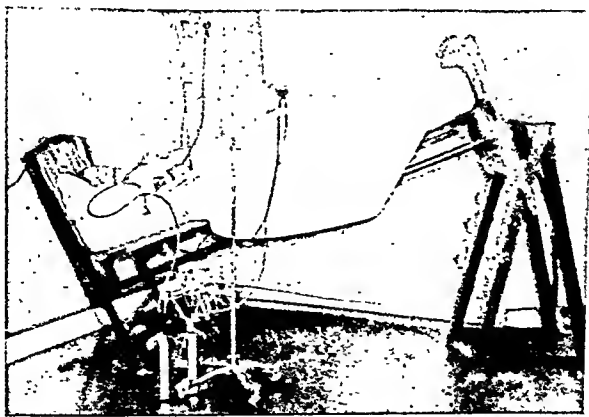


Fig. 16.—Shock frame employed routinely after major abdominal operative procedures. Placement of the patient in steep Trendelenburg position obviates aspiration of mucus or gastric content into the trachea while the patient is asleep. The nasopharynx is kept dry by intermittent suction with an electric pump. When the patient awakens, the foot of the bed may be lowered, but it is kept on the lowest rung for four to five days after operation to prevent venous stasis in the leg veins. (Reproduced from Wangenstein,<sup>6</sup> by permission of *Surgery, Gynecology and Obstetrics*.)

ties of fluid are aspirated from the residual gastric pouch and the afferent duodenal loop, 9 Gm. of sodium chloride a day is ample. Enough fluid should be given by vein or subcutaneously to insure a daily output of urine of 700 to 800 cc. a day (see section on preoperative preparation). Inasmuch as a large number

of these patients have difficulty in voiding because of the age factor, an indwelling catheter is put into the bladder arbitrarily; this permits accurate measurement of the twenty-four hour output of urine. After the initial dose of a sulfonamide compound (3 Gm. of sulfathiazole) implanted at operation, no more is given for forty-eight hours. Then 0.5 Gm. of sulfadiazine is given subcutaneously twice a day as long as the urethral catheter remains in place. All patients are weighed carefully the morning before operation and also each morning through the early postoperative period. This expedient constitutes the best gage of the status of hydration, especially in oliguric patients.

6. In the absence of complications, granted the patient is not too feeble, he is ready for dismissal ten days after operation. And, as a rule, most of our patients undergoing partial gastrectomy for ulcer and a large number of patients undergoing resection for gastric cancer or partial colectomy with primary anastomosis for lesions in the large bowel are dismissed ambulant at that time, with instructions to come to the outpatient clinic for observation within a week, before finally returning to their homes. However, many patients operated on for gastric cancer are too weak to leave the hospital on the tenth postoperative day.

With careful preoperative preparation and well controlled management during and after operation complications are few. If the operative procedure is made to simulate physiologic sleep, there appears to be no direct correlation between the hours spent by the patient in the operating room and his postoperative stay in the hospital. Only 14 patients of the resection group in this series were dismissed within ten days after operation. Twenty-three were dismissed by the fourteenth day. Excluding the 2 patients who underwent total gastrectomy, whose convalescence was longer because of subphrenic abscess, only 1 patient among the survivors was hospitalized for more than eighteen days after operation. In this patient an infection of the urinary tract developed, which kept him in the hospital thirty-one days after operation.

The complete disappearance of postoperative gastric retention (see section on operation, item 11) has been a great aid to quick recovery of the patient. It is a source of constant wonder to me that motor transport in the upper reaches of the gastrointestinal canal appears to be entirely normal for solid food a few days after complete revision of the normal anatomic relationships.

Another hitherto rather common postoperative complication which is giving every evidence of becoming very infrequent after resections of the stomach and colon in this clinic is atelectasis and pneumonia. Occasionally a relatively large number of gastrointestinal resections is done consecutively without either atelectasis or pneumonia being encountered. Why these complications are observed far less commonly now than a few years ago is not wholly clear. I believe that two important causes predispose to postoperative pneumonia: 1. Regurgitation from the stomach into the lungs may occur. This can be prevented by employment of an indwelling gastric suction tube *before, during and after* operation. Use of the Trendelenburg position and the electric suction apparatus immediately after operation to aspirate mucus from the nose, mouth and pharynx is an important prophylactic measure against both atelectasis and pneumonia. 2. Too rapid administration of too much fluid invites cardiac failure, pulmonary edema and pneumonia, especially in patients in the upper age brackets.

The use of the intratracheal catheter, with a balloon to provide a closed respiratory system and frequent aspirations of the mouth and pharynx as well as the bronchi through the intratracheal catheter by the anesthetist during operation, probably also diminishes the opportunity for lodgment of mucous plugs

in the bronchi with ensuing atelectasis. The work of Nungester and Klepser<sup>15</sup> (1938) bears out this suggestion. During early convalescence hyperventilation with a mixture of carbon dioxide and oxygen is carried out several times a day. Probably more important, however, in the prevention of atelectasis is the practice of having the patient give several successive forced coughs every two hours when awake with his lower costal margins supported firmly by the nurse. And finally, the sulfonamide compounds may play a helpful role in thwarting the occurrence of pneumonia, when small mucous plugs in the bronchi may predispose toward its development.

#### TECHNIC OF EXCISION OF EXTENSIONS INTO THE LIVER

Hemorrhage from hepatic tissue is not difficult to control. After the first partial hepatectomy carried out with the cautery, it was believed that a wire loop, employed like a tonsil snare attached to a surgical diathermy unit, would serve the purpose well. A coagulating current was applied to the lung tourniquet, the agent employed to tighten the wire loop. For areas less accessible for use of the wire loop, it was proposed to scoop out successive areas with the loop with employment of the cutting and coagulating current.

These refinements were found not to be particularly helpful. I have therefore reverted to use of the cautery, placing hemostats on large intrahepatic vessels as they are encountered. After these vessels are tied, a small gauze sponge is left on the surface of the liver. Later, during the final moments of the operation, after completion of the resection, invariably it is found that the sponge has attached itself intimately to the cut surface of the liver and is detached only with difficulty, a circumstance similar to one well known to housewives, who find it necessary to surround sliced liver in the ice box with waxed paper (or put it in a glass container) to keep it from sticking to adsorbent surfaces. Thrombin and muscle have been found useful in controlling oozing. In the main, however, the problem of bleeding from cut hepatic tissue has been far less formidable than it was believed to be initially.

The entire left lobe of the liver can be excised by use of the cautery with ease. As yet I have had no occasion while undertaking gastric resection for cancer to excise a large portion of the right lobe of the liver. However, I have removed a fairly large portion of liver tissue at the ligamentum teres, removing a segment of the right and left lobes. If the adjacent edges of hepatic tissue cannot be approximated, the colon may be mobilized to cover the raw edges, the mesentery being stitched to the edges of liver to produce a closed space; drainage of this space with a small tube will direct the temporary escape of bile to the outside. Such biliary fistulas become sealed with the colon and mesocolon and close rather promptly.

Such removal of direct hepatic extension occasioned by invasion of the tumor from the stomach demands no explanation. It is a simple and feasible procedure. Two of the 4 patients for whom partial hepatectomy was done coincidental with partial gastric resection are well and give no evidence now of having any residuals. Twenty months has passed since 1 of them was operated on, and the patient is 40 pounds (18 Kg.) heavier than his preoperative weight and is working regularly. Another man, of 75 years, from whom a large wedge of hepatic tissue was excised from the right and left lobes, is also well twelve months after operation.

<sup>15</sup> Nungester, W. J., and Klepser, R. G.: A Possible Mechanism of Lowered Resistance to Pneumonia, *J. Infect. Dis.* 63:94-102, 1938.



The 2 remaining patients probably have recurrence on the basis of incomplete removal of other extragastric extensions at the time of operation.

To a few patients with cancer of the colon in whom a few isolated hepatic metastases were found in a lobe of the liver in the course of partial colectomy, I have proposed going back after the lapse of two or three months to remove that section of the liver—in the manner in which one would propose dealing first with the local lesion in cancer of the lip and subsequently with the involved regional lymph nodes. The time interval here should probably be a little longer than the usual interval with the lip operation. As yet, however, no patient has accepted the proposal. I have resected the colon in the presence of hepatic metastases a number of times and have been astonished to note how frequently the patients survive for a year. One patient with hepatic metastases from a carcinoma of the small bowel dealt with by operation has been followed in this clinic for four years. The hepatic metastases were not removed, and the patient's weight continues at 70 pounds (32 Kg.) more than his weight at operation. It is to be admitted that survival for a year after gastric resection done for a malignant lesion in the presence of hepatic metastases is unusual. Assuming that the local lesion has been excised completely, one could justify, under otherwise favorable circumstances, secondary entry to excise a portion of the liver in which a few isolated hepatic metastases were noted at operation. Granted that the primary lesion has been excised completely, the only source of further extension would be growth of the hepatic metastases. Probably these conditions are unusual and matters for contemplation rather than situations which the surgeon will have to concern himself about very much. In cases of colonic cancer, secondary extirpation of metastases in a single segment of the liver is, I believe, a justifiable undertaking, in the light of the long survivals attending removal of the local lesion. Further, such secondary partial hepatectomies will afford some information concerning the mode of spread of metastatic cancer within the liver—information which cannot be obtained as long as the local lesion remains *in situ*.<sup>16</sup>

#### TOTAL GASTRECTOMY

Somewhat more than two years ago, I did a succession of total gastrectomies without particular immediate incident. However, the late development of subphrenic abscess in a number of the cases (see section on complications) soon dispelled the thought that total gastrectomy might be done with a risk not out of line with that of partial resection for gastric cancer. Total gastrectomies were done on 2 patients in the present series, in both of whom subphrenic abscess developed.

The schemes of operation suggested by Roscoe Graham<sup>17</sup> (1940) and Morton<sup>18</sup> (1942) probably offer the best protection against the development of subphrenic suppuration. As a matter of fact, a method for total gastrectomy not unlike that of Graham was proposed and described by me in 1937.<sup>19</sup> When the closed method

16. It may even be justifiable for the surgeon to ask whether partial hepatectomy might not be worth while in cases of cirrhosis. Normally, the best stimulus to regeneration of hepatic tissue is to excise a part of the liver. If cirrhotic liver can regenerate, the only considerations which should deter the surgeon are: (1) the question of portal hypertension and the matter of increasing the resistance to inflow of portal blood through the liver and (2) the poor tolerance to operation of patients with cirrhosis.

17. Graham, R.: *Technique for Total Gastrectomy*, *Surgery* 8:257-264, 1940.

18. Morton, C. B.: *Total Gastrectomy: Technical Considerations*, *Surg., Gynec. & Obst.* 75:369-373, 1942.

19. Wangensteen, O. H.: *High Gastric Resection in Cancer of Stomach with Relation of Personal Experience*, *Journal-Lancet* 57:1-4, 1937.

of anastomosis was adopted in this clinic, it seemed to me that encompassing the esophagojejunal anastomosis within the afferent and efferent limbs of the jejunum to prevent fistula formation was unnecessary. My more recent experience with total gastrectomy suggests that burying the site of the esophagojejunal anastomosis within the confines of the adjacent jejunal limbs ascending to and descending from the anastomosis is a very worth while maneuver. In completing the dissection for the esophagojejunal anastomosis, the blood vessels coursing over the fundic end of the stomach are interrupted, and this undoubtedly in many instances comprises the blood supply to the infradiaphragmatic portion of the esophagus.

TABLE 1.—Types of Operation and Hospital Mortality

	Number of Cases	Hospital Deaths	Cases of Recovery
1. Exploration and jejunostomy.....	2	0	2
2. Gastrojejunostomy.....	5	0	3
3. Gastric resections.....	56	3	33
a. Carcinoma.....	53		
b. Lymphosarcoma.....	1		
c. Leiomyoma.....	2		
4. Total gastrectomy.....	2	0	2
Totals.....	43	3	40

Resection mortality, 7.8 per cent.  
Resectability rate, 88.2 per cent.

TABLE 2.—Analysis of Cause of Death in Fatal Cases

Date of Operation	Initials, Age, Sex	Extent of Operation	Survival Period	Cause of Death	
				Unavoidable	Avoidable
1. 9/5/41	A. E. 67 years Male	80 per cent gastric resection and excision of segment of transverse colon with primary anastomosis	6 days	Coronary thrombosis	
2. 10/25/41	E. P. 71 years Female	80 per cent gastric resection, excision of portion of pancreas	48 hours	.....	Fatty liver, pneumonia
2. 3/23/42	E. F. 51 years Male	99 per cent resection, leaving only tiny wedge of very apex of gastric fundus about 1 cm. in length and 5 cm. in width	57 days	.....	Peritoneal abscesses caused by having left a sponge in the peritoneal cavity

## OPERATIVE MORTALITY

All deaths in the hospital after operation are reckoned in computing the operative mortality. The results are indicated in table 1. The mortality in the total group was 7 per cent; in the resection group, 7.8 per cent. It is to be noted (table 2) that there was only 1 unavoidable death. The character of the resections undertaken is indicated in table 3. In this series the gastric resections were done by six surgeons. The larger number, however, were done by two surgical residents and myself.

I have made three previous reports on operative mortality in the surgical management of carcinoma of the stomach. Two years ago<sup>6</sup> in a group of 35 cases of gastric cancer the resection rate was 88.5 per cent and the resection mortality was 11.5 per cent (see table 1 and footnote on page 276 in the 1941

report<sup>20</sup>). The closed anastomosis was used in all cases in both series. In 1937, a report was made covering a thirty month period from July 1933 to January 1936. The resection rate was only 28.5 per cent. During that period, I did only 12 resections for carcinoma of the stomach, with 1 death (8.5 per cent mortality). Prior to July 1933, my experience with a high resection rate for gastric cancer had not been good. As the recent study of Livingston and Pack<sup>1</sup> indicates, very few surgical clinics in this country could then boast of a satisfactory operative experience with the surgical management of carcinoma of the stomach. Chastened by the sobering effect of a study of those results and the criticism of my colleagues, I determined to limit attempts at resection to distinctly favorable cases of cancer with the happier but more contracted experience just related. Emboldened by

TABLE 3.—*Extent of Gastric Resection*

	Number of Cases	Hospital Deaths	Cause of Death
1. Total gastrectomy .....	2	0	
2. 99 per cent resection.....	1	1	See case 1, table 2
3. 98 per cent resection.....	1	..	
4. 95 per cent resection.....	1	..	
5. 92 per cent resection.....	1	..	
6. 90 per cent resection.....	9	..	
7. 85 per cent resection.....	3	..	
8. 80 per cent resection.....	11	2	See cases 2 and 3, table 2
9. 75 per cent resection.....	8	..	
10. 65 per cent resection.....	1	..	
Totals.....	38	3	

TABLE 4.—*Simultaneous Performance of Procedures in Addition to Gastric Resection*

	Number of Cases	Deaths	Cause of Death
1. Partial hepatectomy .....	2	0	
2. Partial hepatectomy and splenectomy.....	1	0	
3. Partial hepatectomy and excision of previous gastrojejunostomy .....	1	0	
4. Simultaneous excision of portion of pancreas.....	1	1	Fatty liver
5. Simultaneous excision of previous gastrojejunostomy.....	1	0	
6. Simultaneous excision of gallbladder.....	1	0	
7. Simultaneous cholecystostomy .....	1	0	
8. Simultaneous repair of paraduodenal hernia.....	1	0	
9. Closure with open duodenum owing to duodenal extension.....	2	0	
10. Simultaneous resection of transverse colon.....	3	1	Coronary thrombosis
Totals.....	14	2	

that experience, I again considerably extended the indications for resection. In the subsequent period (Jan. 1, 1936 to Nov. 1, 1939), covered by the report of 1940,<sup>20</sup> the resection rate had mounted to 70.9 per cent, 39 resections in 55 patients operated on. Extending the operability beyond the generally accepted orthodox indications for resection also increased the mortality materially—8 deaths in 39 cases of resection, a mortality of 20.5 per cent.

It has been very gratifying to note, therefore, that during the last three years the resection rate has gone still higher, but with a distinct lessening of the mortality. The closed resection has, in my opinion, been an important factor in the reduction of that mortality. Four additional technical features deserve mention: (1) use of the left subcostal incision and fine silk sutures instead of catgut, with com-

20. Wangenstein, O. H.: The Surgical Management of Carcinoma of the Stomach. *Minnesota Med.* 23:210-215, 1940.

plete elimination of the hazards of evisceration; (2) safe and secure closure of the blind end of the duodenum, with elimination of deaths from poor inversion; (3) avoidance of postoperative obstruction at the efferent outlet, with complete disappearance of all symptoms or objective evidence of obstruction at the efferent gastric outlet, and (4) avoidance of a closed duodenal loop at the afferent gastric inlet by use of the intubing duodenal tube threaded into that loop from the residual gastric pouch at the time of operation (fig. 11). The last-mentioned complication is not frequent, but it is a potentially serious one.

There are a few other items which have contributed in an important manner to more uniform success in bringing substandard risk patients safely through operation: (1) improved anesthesia; (2) elimination of the element of hurry in the operation (some years ago gastric resections were done regularly in this clinic in one and a half to two hours; since my associates and I have ceased to ask "How long?" but ask instead "How well was the operation done?" more survivals have been entered in the ledger of successes and failures); (3) practical elimination of pneumonia and atelectasis as a frequent postoperative complication and generally improved postoperative care, and (4) improved preparation of the patient, especially with reference to proper feeding.

#### COMPLICATIONS

The only serious complications in the resection group occurred in the 2 patients on whom total gastrectomy was done. In both of these subphrenic abscess developed. One of them had a temporary esophagojejunal fistula as well. In both instances response to drainage of the subphrenic abscess was satisfactory. As Carter<sup>21</sup> (1939) has indicated, when subphrenic abscess forms after gastric resection it is found almost invariably beneath the left side of the diaphragm.

Roentgenograms are taken with use of opaque markers on the skin. Anteroposterior and lateral films without barium and anteroposterior and lateral films with barium sulfate, one taken with the patient sitting and the other when he is in a steep Trendelenburg position, suffice to indicate: (1) whether an abscess is present and (2) where it may be reached most readily. Ordinarily, I drain a subphrenic abscess on the left side through an incision just above the left inferior costal margin. The ninth and tenth costal cartilages are removed, together with almost a centimeter of the rib. An incision is then made through the posterior perichondrial beds. The diaphragm may be incised at this level, or one may dissect up over the diaphragm, opening both diaphragm and peritoneum over the area of induration—which site gives the clue concerning the likely location of the abscess. This is a simple extraserous method of draining a subphrenic abscess, a method which suggests itself readily to the surgeon given to a study of pictorial anatomy. The method, I find, is not new, having been employed by French surgeons during the last century. Lannelongue<sup>22</sup> described its use in 1887. Canniot<sup>23</sup> worked out the anatomic details in 1891. And in 1902 Lejars<sup>24</sup> wrote a comprehensive paper concerning modes of surgical attack on subphrenic abscess. In German surgical literature, this extraserous method of draining subphrenic abscess had

21. Carter, B. N.: Left Subphrenic Abscess, *Ann. Surg.* **110**:562-577, 1939.

22. Lannelongue: Les abcès tuberculeux périhépatiques et leur traitement. *Semaine méd.* **7**:235, 1887.

23. Canniot, E.: De la résection du bord intérieur du thorax pour aborder la face convexe du foie. Thesis, no. 101. Paris. G. Steinheil, 1891.

24. Lejars, F.: Les suppurations de la zone sous-phrénique. *Semaine méd.* **22**:97, 1902.

been described by Melnikoff.<sup>25</sup> Ochsner and his associates<sup>26</sup> have given much study to the general problem of subphrenic abscess.

In the main, the supracostal extraserous method described herein is a satisfactory way in which to drain most subphrenic abscesses on the left side, as well as some on the right side. One of the drawbacks of the method became manifest in 1 of the 2 patients on whom total gastrectomy was performed. Drainage through a supracostal incision on the left side had been made. Because fever failed to abate completely, a posterior drainage was made. The Penrose drain placed at the time of the first procedure was found within the abscess cavity at the second operation. Posterior drainage affords the advantage of continuous dependent drainage.

It seems somewhat strange that this relatively simple method of draining a subphrenic abscess should not merit description in most textbooks on abdominal surgery. The only textbook in which I have noted its description is Spivack's<sup>27</sup> book on abdominal operations. Another possible deterrent which may have dissuaded the French surgeons from continuing the operation is the drainage of pus over exposed cartilages. The development of chondritis has not been observed with this method of draining a subphrenic abscess in this clinic; it is, nevertheless, a possibility.

#### EARLY DEATHS IN RESECTION GROUP SUBSEQUENT TO DISMISSAL FROM THE HOSPITAL

Six patients are known to have died after dismissal from the hospital. Five of these died of cancer. The other patient, a dyspneic man of 60 with a low vital capacity from an occupational silicosis, died two months after operation of lobar pneumonia. His physician reported that no residual malignant growth was found at autopsy. Two of the 5 persons who died of cancer were patients with pernicious anemia, who had hepatic metastases at the time of operation; one survived one hundred days and the other one hundred and twenty-three days. A patient with invasion of the duodenum necessitating inversion with an open duodenum (fig. 5) died two months after operation. Another patient, in whom a 90 per cent palliative resection was done for a tumor adherent to the pancreas and transverse mesocolon, died four months after operation. The remaining patient known to be dead had a total gastrectomy and died approximately five months after operation.

Two additional patients have obvious evidence of recurrence—one at six months and the other at nine months after the operation. One additional patient presents presumptive suggestions of recurrence nine months after operation. In addition, there are a few patients who continue well despite microscopic evidence of cancer at the line of resection, in whom recurrence may be expected.

The enumeration of these circumstances affords little encouragement to the surgeon who proposes to improve the status of the patient with a late or far advanced gastric cancer. Yet in many such instances surgical intervention is necessary to arrest vomiting and prevent death from thirst and starvation. Without an aggressive surgical attitude toward the problem of gastric cancer, the incidence of ultimate cures will be limited to the distinctly favorable cases. In any case, obviously, the larger number of cures will always come out of that group. Yet, if

25. Melnikoff, A.: Die chirurgischen Zugänge durch den unteren Rand des Brustkorbes zu den Organen des subdiaphragmalen Raumes, *Deutsche Ztschr. f. Chir.* **182**:83-151, 1923.

26. Ochsner, A., and Graves, A.: Subphrenic Abscess: An Analysis of 3,372 Collected and Personal Cases, *Ann. Surg.* **98**:961-990, 1933.

27. Spivack, J. S.: *The Surgical Technique of Abdominal Operations*, Chicago, S. B. Debour, 1936.

formal resection can be extended to the patients with advanced cancer as only a palliative procedure without great increase of risk over that presented by exploration or gastrojejunostomy, the additional salvage in length of survival and increased comfort should be worth the extra expenditure of time and effort.

#### LATE RESULTS

My associate Dr. George S. Bergh<sup>28</sup> began some years ago a follow-up of the patients who had survived gastric resection in this clinic. In 1939 he found that 57 patients had survived operation for carcinoma of the stomach and were well without evidence of return of the disease for fairly long periods, up to more than ten years after operation. Continuance of that study was interrupted by the war, and the pressure of many obligations on a depleted hospital staff precludes bringing Dr. Bergh's study of earlier resections for gastric cancer up to date at this time.

#### SUMMARY

Carcinoma of the stomach is one of the most serious of all surgical disorders and takes a large toll of life. A large proportion of patients with gastric cancer continue to come to the surgeon too late to be benefited by operation. Of patients not already presenting evidence of inoperability, the majority of those submitted to surgical exploration can have the lesion resected with a reasonable risk. However, in any such group there are bound to be a fair number of palliative resections, unless the surgeon is constrained to limit gastric resection to the favorable cases only. In the main, palliative resections for gastric cancer do not prolong life as much as similar operations undertaken for colonic cancer. Nevertheless, as long as palliative operations can be done with reasonable risk, it is preferable to excise the ulcerative lesion, even though the betterment is only temporary. The surgeon should excise the entire lesser curvature routinely in all operations for gastric carcinoma, to avoid leaving residual microscopic cancer at the proximal line of resection. The resection rate in the group of 43 cases reported was 88.2 per cent. The hospital mortality was 7 per cent and the resection mortality 7.8 per cent. Two of the 3 hospital deaths in the present group were avoidable.

The closed anastomosis is employed regularly in all resections in the gastrointestinal canal in this clinic. The experience of this clinic with its use suggests that it is an item of some importance in extending resection to patients who are substandard risks without increasing the hazards of operation. The loss of blood during operation should be minimal. Employment of dry sponges and of the weighing scale teaches the surgeon and his staff that slight upsets of the bodily economy during operation are well tolerated by the patients. Restorative fluids given to offset the upsets wrought by the surgeon should be given by precision technique—neither too much nor too little. The weighing scale constitutes the best and most reliable index of the amounts necessary. A well planned operative procedure should simulate physiologic sleep—recovery from the patient's illness commencing with the beginning of the operation. Operative procedures which test the patient's capacity to tolerate great fluctuations in vital functions also tax his ability to withstand them. The outcome of such procedures is unpredictable. The planned operation leaves nothing to chance, and the risk assumed for the patient is susceptible of measurement.

<sup>28</sup> Bergh, G. S.: Seminar Discussion on Carcinoma of the Stomach, *Lancet*, 1951, unpublished data.

Complete elimination of postoperative obstruction at the efferent gastric outlet after resection has been an important item in reducing operative hazards, morbidity and mortality. The somewhat improved showing in the present series over that of two years ago has been achieved essentially by better preoperative management. It is hoped that eventually the disparities of risk in gastric resection for ulcer and for carcinoma will be largely erased. It is likely, however, that this objective can never be achieved entirely unless the resection rate is reduced.

Hepatic resection is a justifiable procedure for the excision of direct carcinomatous extensions from the stomach into the liver. Four such operations were done in the group of patients reported on—all without particular incident. It is suggested that in cases of colonic cancer it may prove feasible to do a secondary hepatic resection for isolated hepatic metastases in otherwise favorable cases a few weeks after the excision of the colonic lesion. One instance is reported herein in which para-aortic lymph nodes were removed coincidentally with gastric resection. It is indicated also that any other necessary surgical procedure, such as excision of a diseased gallbladder or repair of a hernia, may be undertaken simultaneously, apparently without pyramiding the risk to the patient.

The importance of adequate preoperative preparation of poor risk surgical patients to withstand formidable operations cannot be stressed too much. The feeding of a liberal portion of protein with good capacity to bring about regeneration of plasma protein combined with a high carbohydrate and low fat diet combats the fatty liver diathesis of starvation and repairs hypoproteinemia simultaneously. Many substandard risk patients have to be given this diet by intragastric drip feeding, day and night. A well planned postoperative ritual following a well executed operative procedure should eliminate most of the ordinary postoperative complications, including distention, pneumonia and embolism.

Lasting cures of gastric cancer can be achieved only when complete operations are done. If patients with gastric cancer do not come to operation in larger numbers in an earlier stage of the disease, there will not be a high proportion of lasting cures among those on whom resection is done.

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# TOTAL GASTRECTOMY FOR CARCINOMA OF THE STOMACH

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The patient who harbors a gastrointestinal carcinoma is doomed unless the growth is removed by a surgical operation. The contraindications for the removal of such a primary growth are decreasing. The primary lesion is being removed with increasing frequency because of a constantly decreasing primary mortality. Two questions must be answered:

1. What is responsible for the decrease in the primary mortality?
2. Should one remove the primary malignant lesion if it is impossible to eradicate all gross evidence of the disease, such as metastases in the liver or in the regional lymph glands?

The lowering of the primary operative mortality of gastrointestinal carcinoma is not due solely to an extensive surgical experience coupled with a perfection of surgical technical procedures. Superb technical skill avails little if the patient's condition is such that he cannot tolerate without disaster the necessary operative procedure. The surgeon must pay tribute and acknowledge his debt to the fundamental scientists. They have accumulated and presented data revealing the biochemical and physiologic disturbances which accompany serious gastrointestinal disease. Clinicians have been tardy in applying to clinical practice the lessons learned in the laboratories. The most recent application of the laboratory studies in nutrition relates to the administration of protein. For some time clinicians have recognized and corrected the biochemical imbalance due to dehydration, hypochloremia, avitaminosis and carbohydrate depletion, but the significance of a deficiency of protein had until recent years rarely been either recognized or corrected. Since the discovery of the need for protein the preparation of patients with nutritional disturbances resulting from gastrointestinal disease has been greatly improved. The readily available protein afforded by blood or plasma banks and in the form of hydrolyzed casein has been of inestimable value in restoring and maintaining by parenteral routes the adequate protein metabolism so necessary to the preoperative preparation of patients suffering from gastric carcinoma which demands an attempt at total gastrectomy.

The wisdom of removing a local malignant lesion in the presence of irremovable metastases is debatable. However, the case for removal is supported by the fact that if the local lesion is removed the comfort of the patient, both mental and physical, is greatly increased. Further, all surgeons have noted that in an unpredictable number of instances the progress of the residual disease seems to have been definitely retarded after the removal of the primary lesion since some patients have survived a much longer time than one would have anticipated. Thus no criticism could be directed at removal of a primary growth if it could always be removed without primary mortality. However, in instances in which the local extent of the carcinoma demands a total gastrectomy, the primary mortality which still attends this procedure is so great that it is extremely doubtful if a total gastrectomy should be carried out in the presence of obvious irremovable metastases. This opinion, however, will be modified by the philosophy of the individual surgeon.



by the extent of the irremovable metastases and by the age and general condition of the patient. While it is true that most patients with gastric carcinoma which demands a total gastrectomy will, if they survive long enough, ultimately die of recurrence of the carcinoma, it is possible in the majority of cases to give definite mental as well as physical relief to the patient during the survival period. Acceptance of the responsibility to give mental as well as physical relief will also be a factor which will determine the enthusiasm of the individual surgeon for the total removal of the stomach.

Gastric carcinoma is not, as so many patients and indeed a few physicians believe, a hopeless disease. All surgeons who have interested themselves in gastric carcinoma for many years can recall survivals of fifteen years or longer after partial gastrectomy for carcinoma; and if the primary operative mortality of total gastrectomy can be lowered, it may become possible to present patients who have survived for a surprisingly long time free from recurrence. My own attitude is that whenever possible, unless the metastases are gross or other factors deter, one should carry out a removal of a gastric carcinoma even though total removal of the stomach may be necessary.

Although the application of scientific data to the preoperative correction of nutritional disturbances makes possible the total removal of the stomach for patients who previously would have been denied this opportunity for survival, there is still a forbiddingly high primary operative mortality, which, as has been shown at autopsy, is due to technical defects in the operative procedure. After much thought and many studies, with various combinations of operative procedures, a technic for total gastrectomy which has to a great degree overcome the defects and disasters of all my previous efforts is now being used.

The details of the operative procedure I am now using are as follows: After adequate preparation the patient is sent to the operating room with a Levine tube in the stomach and an intravenous infusion of physiologic solution of sodium chloride and 5 per cent dextrose being administered by the drip method. Intermittent spinal anesthesia is used, based on the technic advocated by Lemmon.<sup>1</sup> Nupercaine hydrochloride is used as in induction of ordinary spinal anesthesia, but the special malleable metal spinal needle and the special mattress suggested by Lemmon are employed. If the operative procedure is prolonged beyond the time which former experiences have shown to be accompanied by an adequate anesthesia from nupercaine alone, a previously prepared solution of procaine hydrochloride in spinal fluid is injected as the supplementary anesthetic. There is the greatest satisfaction from this scheme of anesthesia. I have completely overcome my original horror at the thought of a needle's being continuously in the spinal canal for two hours or longer during the course of a difficult abdominal operation. One avoids the anxiety and mental turmoil of the surgeon and the increased hazard to the patient which are the inevitable accompaniment of supplemental inhalation anesthesia which becomes necessary when the spinal anesthesia wears off before the completion of the operative procedure. If the patient becomes restless or is awake and apprehensive during the operation, the intravenous infusion already in progress permits the intravenous administration of sodium pentothal in a concentration of 2.5 per cent. This is very efficient in quieting the patient. By this same route one can readily administer stimulants, as well as blood or plasma, should such be necessary. This technical modification of Lemmon's method,<sup>1</sup> which has been worked out by Dr. W. Easson Brown.<sup>2</sup>

1. Lemmon, W. T.: A Method for Continuous Spinal Anesthesia, *Ann. Surg.* **111**:140-145 (Jan.) 1940.

2. Brown, W. E.: Personal communication to the author.

a member of the anesthetic staff of the Toronto General Hospital, has resulted in a diminution of the operative shock and the undertaking of prolonged and difficult procedures with greater safety to the patient than was possible previously.

The abdomen is opened by splitting the right rectus muscle just to the right of the midline. If the incision is carried high enough so that the peritoneum can be opened to the level of the xiphoid cartilage, I have been impressed with the value of such a high incision in giving an adequate exposure. On occasions the left abdominal wall is divided laterally, the incision starting at a point midway between the xiphoid process and the umbilicus and dividing the rectus muscle transversely. There is no contraindication to this supplementary transverse incision, but it is not always necessary. A careful survey of the intraperitoneal contents for remote metastases, particularly in the pouch of Douglas, should be the primary maneuver. While one need not necessarily withhold a radical total gastrectomy in the presence of minimal metastases, it is imperative to assure oneself that the result is worth the risk under such circumstances. The hazard of a total gastrectomy is much greater than that which accompanies the removal of an extensive carcinoma of the colon or the rectum. Removal of a local lesion of the colon or the rectum is accompanied by such constant and great relief of symptoms that excision is justifiable in the presence of extensive metastases. Similar metastases from carcinoma of the stomach would preclude total gastrectomy.

When it has been decided that a total gastrectomy is desirable and possible, the first procedure is the mobilization of the left lobe of the liver by the division of the peritoneal attachment. This procedure, popularized by Grey Turner,<sup>3</sup> gives adequate exposure and access to the entrance of the esophagus to the peritoneal cavity. The great omentum is then removed in its entirety from the attachment to the colon. If the assistant holds the omentum in one hand and the colon in the other, so that tension is maintained on the tissues at the junction of the omentum with the colon, the entire maneuver of removing the omentum from the colon can be carried out through an avascular plane with the use of surprisingly few hemostats and with little trauma to the tissues and loss of blood.

The mobilization of the greater and lesser curvatures of the stomach, with division of the duodenum and closure of the duodenal stump, is then carried out. The details of this maneuver have been presented previously<sup>4</sup> as part of the procedure necessary in gastric resection for ulcer. It is advantageous after the duodenum has been divided to wrap the stomach in a gauze pad and tie the pad in position with a stout tape. A finger is then inserted through the diaphragm beside the esophagus (fig. 1). Using the stomach as a handle and with downward traction on the esophagus, one can mobilize the lower end of the esophagus to a remarkable degree. During this procedure both vagus nerves are identified and isolated. The division permits a further mobilization of the esophagus. The separation of the periesophageal tissues by blunt gauze dissection will often make it possible to draw down the esophagus until 2 inches (5 cm.) or more will lie below the diaphragm. When one has delivered below the diaphragm as great a length of esophagus as seems safe and possible, a point is selected on the jejunum sufficiently remote from the fixed duodenojejunal junction to permit the approximation of the jejunum to the diaphragm behind the esophagus without any tension on the mesentery of the jejunum. The suggestion of Allen<sup>5</sup> that the jejunum

3. Turner, G. G.: Henry Jacob Bigelow Lecture: Some Experiences in Surgery of Esophagus, *New England J. Med.* 205:657-674 (Oct. 1) 1931.

4. Graham, R. R.: Technical Surgical Procedures for Gastric and Duodenal Ulcer, *Surg., Gynec. & Obst.* 66:269-287 (Feb.) 1938.

5. Allen, A. W.: Total Gastrectomy for Carcinoma of the Stomach, *Am. J. Surg.* 40: 35-41 (April) 1938.

be attached to the diaphragm by interrupted silk sutures is utilized (fig. 1). This excellent procedure anchors the jejunum in such a manner as to prevent a strain on the esophagojejunal anastomosis by the weight of the jejunum and its contents. After the jejunum has been securely anchored to the diaphragm, the esophagus is then sutured to the anterior surface of the distal limb of the jejunum by interrupted silk sutures (fig. 2). Three or four such sutures on each side are usually sufficient. The most distal suture on each side is placed at the level of the proposed anastomosis of the end of the esophagus to the side of the jejunum. These sutures are left long and held with hemostats to act as guy sutures. Holding the guy sutures, the surgeon then turns the stomach up toward the chest, exposing the

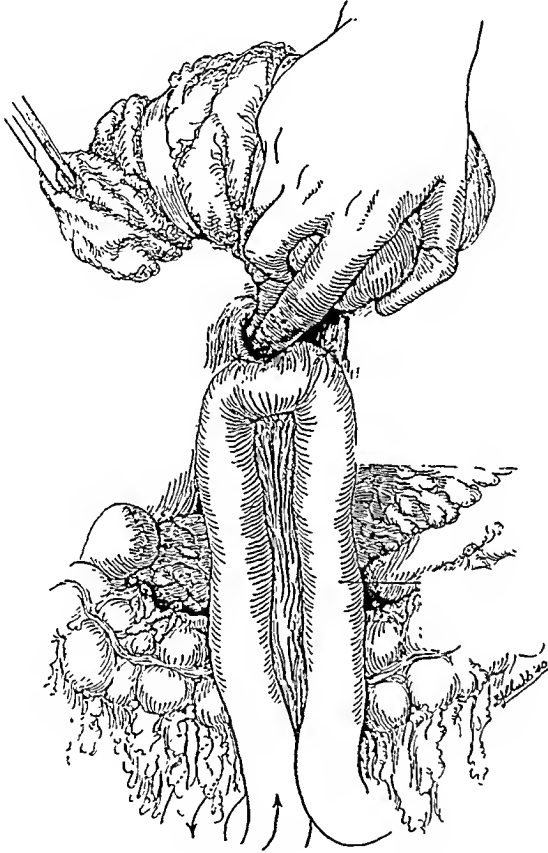


Fig. 1.—The stomach has been divided from the duodenum. The infradiaphragmatic length of the esophagus is increased by freeing it from the margins of the diaphragm by inserting the finger along the esophagus into the mediastinum. The esophagus at a point 18 inches (46 cm.) from the duodenojejunal junction is fastened to the diaphragm behind the entrance of the esophagus by means of interrupted sutures. The illustrations for this article have been previously published (Graham, R. R.: *Technique for Total Gastrectomy*, *Surgery* 8:257-264 [Aug.] 1940.)

posterior wall of the esophagus. Interrupted silk sutures of the Halsted type unite the posterior wall of the esophagus to the anterior wall of the jejunum. (fig. 3A), forming the outside posterior row of anastomotic sutures. The esophagus is now opened. Before it is opened, however, one precaution must be taken. The Levine tube is withdrawn into the esophagus to a point just proximal to the proposed site of division. Continuous suction is then maintained through the Levine tube while the esophagus is being opened. This prevents the escape of oral and eso-

phageal secretions, which obviously are not sterile and which otherwise would flood the site of the anastomosis. A Wertheim right angle clamp is then placed across the stomach at the entrance of the esophagus to prevent any spilling of gastric contents (fig. 2). The jejunum is opened transversely so that a stoma of the same diameter as the esophagus is made. The end to side anastomosis is then completed by suturing the mucous membrane of the esophagus to the mucous membrane of the jejunum (fig. 3*B*). When the posterior layer of the anastomosis is completed, the stomach is amputated. The Levine tube is then passed down into the distal limb of the jejunum well beyond the level of the esophagoduodenal anastomosis (fig. 4*A*.) The anterior suture line is then completed in the usual manner, making a satisfactory end to side stoma between the lower cut end of the esophagus and the anterior wall of the distal limb of the jejunum. While the stomach may be amputated from the esophagus in an earlier phase of the procedure, I have found it an advantage, particularly if there is a short sub-diaphragmatic esophagus, to utilize the stomach as a means of downward traction.

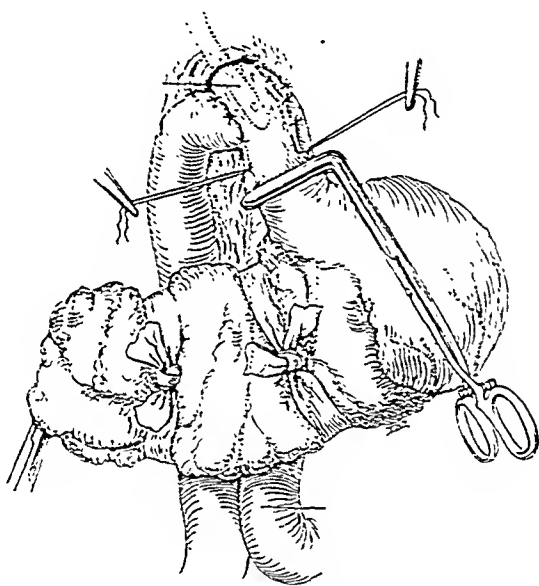


Fig. 2.—The infradiaphragmatic portion of the esophagus is placed on the anterior surface of the distal limb of the jejunum and fastened there by means of interrupted silk sutures. The esophagus is kept free from accumulated secretions by a Levine tube attached to suction apparatus.

In order to reenforce the line of anastomosis and to surround it with a peritoneal covering, the proximal jejunal loop is then rolled laterally across the esophagus and sutured to the left lateral margin of the distal limb of the jejunum (fig. 4*B*). This completely surrounds the infradiaphragmatic portion of the esophagus with the jejunal loops and very firmly covers and supports the anastomosis. This maneuver completely obstructs the proximal jejunal loop, and therefore an enter-enterostomy must be carried out between the proximal and the distal jejunal loop (fig. 4*B*). When the distal limb of the jejunum is opened during the performance of this anastomosis,<sup>6</sup> the Levine tube is grasped and passed well down into the distal limb of the jejunum 12 to 18 inches (33 to 46 cm.) distal to the entero-

6. Graham, in Bancroft, F. W.: *Operative Surgery Including Anesthesia, Pre- and Post-operative Treatment*, New York, D. Appleton-Century Company, Inc., 1941, sect. 10, p. 589.

enterostomy fistula, so that through it nourishment may be delivered directly into the jejunum, obviating the necessity of a jejunostomy. The abdomen then is closed with interrupted figure-of-eight sutures of stainless steel wire, as advocated by Jones.<sup>7</sup> I have found it advantageous to place a stitch in the patient's cheek and tie the Levine tube with this stitch, so that during the immediate postoperative restless period the patient will not inadvertently withdraw the Levine tube.

While one can carry out this technic with either catgut or silk, I have been impressed with the freedom from trauma to the tissues and untoward reactions which accompanies the use of silk sutures to such an extent that I use them in preference to catgut.

It is important to carry into the postoperative period the same meticulous care in maintaining an adequate biochemical nutritive balance as was observed in the

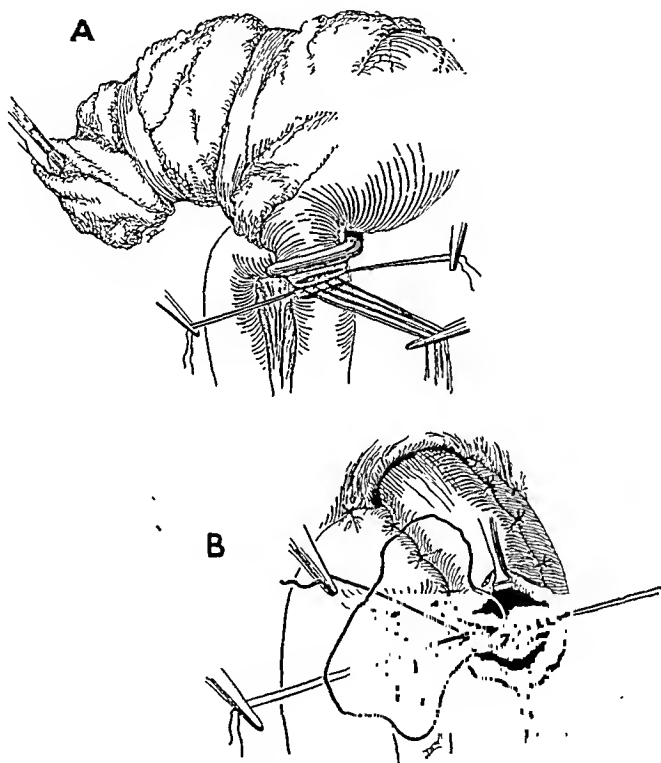


Fig. 3.—*A*, if the infradiaphragmatic portion of the esophagus is unduly short, it is advantageous to leave the stomach attached to the esophagus while interrupted sutures unite the posterior wall of the esophagus to the anterior wall of the distal limb of the jejunum. The two lateral sutures are held in hemostats and act as stay sutures while the esophago-jejunal anastomosis is completed. *B*, the stomach is cut away and the mucous membranes of the stomach and jejunum are being united.

preoperative preparation. While one can administer intravenously sufficient fluid, sodium chloride, protein and carbohydrate to maintain an adequate balance, I have at the end of twenty-four hours dripped through the Levine tube a 10 per cent solution of dextrose in distilled water, at the rate of 125 cc. an hour. At the end of forty-eight hours I begin through the Levine tube the type of feeding and management which I have advocated in the treatment of gastric ulcers.<sup>3</sup>

7. Jones, T.: Use of Alloy Steel Wire in Closure of Abdominal Wounds, *Surg., Gynec. & Obst.* 72:1056-1059 (June) 1941.

My experience in total gastrectomy has been confined to 21 cases. In this group I have had an almost forbidding primary mortality. However, in the last 7 cases I have carried out the procedure suggested, and in only 1 has there been a leak at the site of the anastomosis. This was due to an obstruction of the small intestine at the site of a jejunostomy. This obstruction so dilated the proximal jejunum as to put an undue strain on the suture line, with resulting necrosis, leakage and fatal general peritonitis. This unfortunate experience has led me to abandon the Weitzel type of jejunostomy. I use now when necessary the technical procedure described by Clute<sup>8</sup> and have found it very satisfactory. That it is justifiable to strive tenaciously for the extirpation of gastric carcinoma capable of removal, even if total gastrectomy is necessary, is supported by the fact that among the 21 cases in my series there were 7 in which the disease was confined solely to

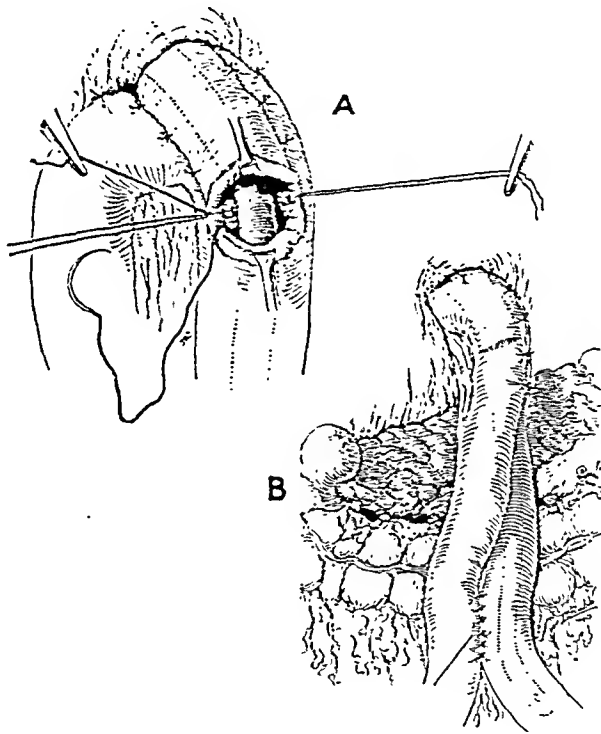


Fig. 4.—A, when the sutures through the posterior layer of mucous membrane are completed, the Levine tube is passed down farther into the distal jejunum well past the esophagojejunal anastomosis, and the anterior layers of the anastomosis are completed. B, the proximal jejunum is then folded over the front of the esophagus and the esophagojejunal anastomosis and united to the lateral margin of the distal limb of the jejunum. By this maneuver the esophagus and the esophagojejunal anastomosis are completely encircled by the jejunal loops. This contact of peritoneum to peritoneum ensures healing to a greater degree than the contact of the bare esophagus to the jejunum. This maneuver completely obstructs the proximal jejunal loop and makes an enteroanastomosis necessary. During the anastomosis the Levine tube is passed farther down into the distal jejunum to make possible direct jejunal feeding early in the patient's convalescence.

the stomach. That is, in 33 per cent, or one third, of the cases which demand total gastrectomy there has been an absence of metastasis even to the regional lymph glands.

8. Clute, H.: Jejunostomy, *Ann. Surg.* **114**:462-471 (Sept.) 1941.

Much debate has centered around the wisdom of a coincident removal of the spleen. There is no doubt that this procedure makes the operation of total gastrectomy technically easier. However, one must not lose sight of the fact that there is a definite change in the concentration of blood platelets after splenectomy. In 1 of my cases a cerebral thrombosis developed on the tenth postoperative day. This resulted fatally, and autopsy revealed no intraperitoneal lesion which could have contributed to the patient's death. I am wondering to what extent the splenectomy was a contributing factor. Thus while I cannot condemn the removal of the spleen, I hesitate to perform splenectomy unless it greatly decreases the difficulty of the operative procedure.

When patients have been operated on in the presence of serious nutritional disturbances, there is a higher incidence of imperfect wound healing and wound disruption than under other circumstances. For this reason I have adopted the method of wire closure of the abdominal wall with figure-of-eight stainless steel sutures, as described by Jones,<sup>7</sup> and they have proved to be most satisfactory. As I have gradually increased the application of this type of wound closure for the undernourished and bad risk patient, I have become more enthusiastic with the procedure. I have found that if one places all the sutures before tying any, the incidence of breakage of the steel sutures when they are being tied can be decreased to the minimum. The freedom from irritation to the wound and the fact that it will heal without a sinus even in the presence of a moderately severe infection have been surprising and delightful.

#### SUMMARY AND CONCLUSIONS

A technical operative procedure is presented which it is hoped will result in a lower primary mortality from total gastrectomy.

Seven of 21 patients on whom total gastrectomy was carried out showed freedom from metastasis in the regional lymph glands.

The correction of nutritional disturbances during the preoperative and the postoperative period contributes greatly to the safety of this procedure.

Survival after total gastrectomy is compatible with happiness, negligible dietetic restrictions and freedom from gastrointestinal distress.

It is suggested that one is justified in tenaciously clinging to the philosophy that gastric carcinoma should be removed, even though total gastrectomy may be necessary.

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## TRANSTHORACIC RESECTION FOR CANCER OF THE CARDIAC END OF THE STOMACH

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CHICAGO

Cancer involving the cardiac end of the stomach may be primary in that location, or it may be secondary by extension from either the cardia of the esophagus above or the body of the stomach below. From a pathologic standpoint there is no fundamental difference between such a tumor and those arising in other portions of the stomach or esophagus. A tumor arising in the cardiac portion of the stomach most frequently begins along the lesser curvature, but it may begin in the fundus either anterior or posterior to the gastrophrenic attachment. The former type is readily detected by roentgenography and gastroscopy, but the latter may be easily overlooked. The tumor may grow until it is of considerable size before reaching the esophagus, but often it begins to encroach on its outlet relatively early and eventually may infiltrate as much as 2 or 3 cm. of its lower end. If a gastric cancer begins distally and grows into the cardiac end, it usually reaches considerable size before producing obstructive symptoms, and the diagnosis may be correspondingly delayed. Cancer of the cardiac or infradiaphragmatic portion of the esophagus, in addition to invading the wall and narrowing the lumen, usually extends to or invades the cardiac portion of the stomach. As in one of the cases to be reported, the amount of tumor in the stomach may be about as large as that in the esophagus. In some cases the overlap of cardiac esophageal cancer on the stomach or of cardiac gastric cancer on the esophagus makes it difficult to determine from clinical, roentgenologic and even gross pathologic examination which structure is the primary seat of the lesion. The decision is made only by microscopic examination of tissue obtained for biopsy or during resection or necropsy, which reveals whether it is squamous cell or columnar cell cancer.

Regional extension of carcinoma of the gastric cardia may be by way of the lymphatics or by direct invasion of the adjacent tissues. Metastases to lymph nodes are most frequently encountered along the upper half of the lesser curvature, and retroperitoneal nodes may be involved, especially if there are retrogastric adhesions. Carcinomatous invasion of the adjacent tissues is most often seen when the tumor is in the posterior wall, in which case there may be tumor nodules disseminated over the peritoneum of the lesser peritoneal cavity or adhesions to and infiltration of the retroperitoneal tissues, including the tail of the pancreas. The spleen or the end of the left lobe of the liver may be fused with the tumor, and when the fundus is involved there may be adhesions to the diaphragm. Nodules are sometimes seen on the upper side of the diaphragm after the chest has been opened. The diaphragm may also be invaded at the esophageal hiatus. The finding at transthoracic operation of fluid in the chest or beneath the diaphragm either in the greater or in the lesser peritoneal cavity is nearly always a contraindication to resection of the tumor. Metastases in the liver and throughout the general peritoneal cavity are similar in frequency to metastases from other gastric cancers.

Primary cancer of the cardia of the esophagus produces metastases to the lymph nodes along the lesser curvature of the stomach with as great regularity

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From the Department of Surgery of the University of Chicago.



as does primary cancer of the cardiac portion of the stomach, since the normal drainage is to those nodes. In addition, it more frequently makes metastases along the posterior mediastinum and in the pleura and the lungs, especially in the advanced stages. It may be directly fused with the diaphragm at the hiatus, but within the abdomen it produces peritoneal nodules and adhesions and metastases in the viscera with less frequency than does primary cancer of the cardiac portion of the stomach. Narrowing of the cardia is of great diagnostic importance, since the resultant difficulty in swallowing is usually the first symptom of cancer of the cardiac end of the esophagus and is a common symptom at some stage of cancer of the cardiac end of the stomach.

Meritorious operations for cancer involving the cardiac end of the stomach are developments of comparatively recent date. They have been performed both by the abdominal and by the thoracic route.

Resection by the abdominal route was carried out with success in advance of that by the thoracic route and in cases in which there is slight or no obstruction of the terminal portion of the esophagus the procedure has become more or less routine in many of the leading surgical clinics. It consists of total gastrectomy and esophagojejunostomy. As examples of the extent to which it is employed and of the success attained with cancer either primarily or secondarily involving the cardiac region of the stomach, Lahey and Marshall<sup>1</sup> have reported 33 total gastrectomies with 9 deaths, and Coller and Farris,<sup>2</sup> 27 operations with 5 deaths.

The drawback to gastrectomy by the abdominal route is in the cases in which the esophagus is involved to such an extent that adequate resection cannot be done without interfering with the performance of anastomosis with the esophagus below the diaphragm. Also in cases of cancer confined to the cardia, the entire stomach is sacrificed, no one seeming inclined to resect the involved portion and anastomose the remaining portion of stomach to the esophagus. The first to lessen these difficulties was Ohsawa,<sup>3</sup> who performed what he styled a laparotomy and semithoracotomy. The abdomen was first opened through an upper midline incision. If the lesion appeared to be operable, a second incision was extended to the left and upward from this over the course of the eighth rib to the angle of the scapula. About 3 cm. of the anterior ends of the seventh, eighth and ninth ribs was resected, and the ninth intercostal space was incised for a length of 5 cm. This was done extrapleurally if possible, but if the pleura was injured no attention was paid to it. The costosternal border was divided, the costosternal arch thus being broken down (Marwedel's mobilization). The costal arch flap was then retracted upward. The suspensory ligament of the left lobe of the liver was cut and the lobe retracted. The esophagus was separated from the diaphragm, and with this retraction it was possible to expose the esophagus in some cases for a length of 10 cm. This permitted resection of stomach and an adequate amount of esophagus, with room for anastomosis. In his report, Ohsawa did not distinguish the carcinomas of the cardiac end of the stomach from those of the terminal portion of the esophagus, but with some of the growths, whether gastric or esophageal, this exposure was found to be inadequate, so that he opened the chest by incising the diaphragm from the front back to the esophageal hiatus. After this procedure the anastomosis could be accomplished.

Altogether 18 patients with tumors of the lower portion of the esophagus, including the esophageal cardia, and 20 patients with tumors of the stomach which

1. Lahey, F. H., and Marshall, S. F.: Combining Splenectomy with Total Gastrectomy, *Surg., Gynec. & Obst.* **73**:341, 1941.

2. Coller, F., and Farris, M. J.: Total Gastrectomy, *Surgery* **13**:823, 1943.

3. Ohsawa, T.: Surgery of the Esophagus, *Arch. f. jap. Chir.* **10**:605, 1933.

involved the cardiac portion were operated on. The 18 tumors of the lower portion of the esophagus and of the cardia were treated by resection and esophagogastronomy, with 8 recoveries. The 20 tumors of the stomach were treated by total gastrectomy and esophagojejunostomy, with 12 recoveries. Despite Ohsawa's failure to divide operations into those performed by what he designated as the semithoracotomy-transabdominal technic or the free thoracolaparotomy technic, it is evident that in some of the successful operations the diaphragm was opened from front to back. Hence he deserves credit for the first successful one stage resection and esophagogastronomy and total gastrectomy and esophagoduodenostomy by means of a combined laparotomy and thoracotomy. This was a decided step forward in the development of resection and anastomosis as the method of treatment of cancers of the cardiac portion of the stomach and the esophagus.

Various two stage operations have been done in which the abdomen was opened and the involved portion of stomach mobilized and in some cases divided. After this the chest has been opened, either during the same operation or subsequently, and resection and anastomosis carried out. These procedures are now of little more than historical interest. Marshall in 1938 reported a successful two stage operation for carcinoma of the terminal portion of the esophagus in which he opened the abdomen, mobilized the stomach proximally and displaced it through the enlarged diaphragmatic hiatus into the chest. At the second stage, several days later, the chest was opened, the tumor resected and an esophagogastronomy performed. This procedure is now sometimes performed in one stage.

#### ONE STAGE TRANSTHORACIC RESECTION AND ESOPHAGOGASTRIC ANASTOMOSIS

Transthoracic resection was performed by Ohsawa in 3 cases. First the chest and then the diaphragm was opened; the lower portion of the esophagus and the proximal portion of the stomach were mobilized; the tumor was resected, and the esophagus and the remaining portion of the stomach were anastomosed by suture. All 3 patients died. In 2 cases Sauerbruch's invagination operation was performed, and 1 of the patients survived. Ohsawa designated this procedure as unreliable because of the danger of perforation produced by the proximal and distal crushings and uncertainty of thereby interrupting the blood supply to the invaginated tumor.

As far as has been determined, the first successful one stage transthoracic resection and anastomosis of the esophagus and stomach was reported by Adams and Pheister<sup>4</sup> in 1938. It was performed Jan. 26, 1938 on a 53 year old woman for a primary carcinoma in the cardiac end of the esophagus with slight secondary invasion of the adjacent stomach and metastases in the lymph nodes alongside the upper portion of the lesser curvature. Approximately 3 inches (8 cm.) of the esophagus and 1 to 2 inches (2.5 to 6 cm.) of the stomach were resected. The stomach end was closed and the end of the esophagus anastomosed by suture to the anterior wall of the stomach—on the basis of previous experimental anastomotic studies by Adams, Escudero, Aronsohn and Shaw.<sup>5</sup> A catheter gastrostomy was performed, a procedure which has since been discontinued. The patient has since remained free from signs of recurrence, and figure 1 shows the roentgenographic appearance five years and three days after the operation. She is active and has

4. Adams, W. E., and Pheister, D. B.: Carcinoma of the Lower Thoracic Esophagus: Report of a Successful Resection and Esophagogastronomy. *J. Thoracic Surg.* 7:621, 1938.  
5. Adams, W. E.; Escudero, L.; Aronsohn, H. G., and Shaw, M. M.: Resection of the Thoracic Esophagus, *J. Thoracic Surg.* 7:605, 1938.

remained well aside from the fact that she sometimes suffers from nausea at night and must eat more slowly than before. A portion of the fundus has dropped tam-o'-shanter-like to the rear and left of the free anastomosis, as is shown in the roentgenogram, and the occurrence of nausea may be related to stagnation within it. There is no regurgitation during recumbency. Peristalsis is visible roentgenoscopically only in the pyloric region.

Ochsner and De Bakey<sup>6</sup> performed the first successful transthoracic resection and anastomosis of a carcinoma of the cardiac end of the stomach Sept. 22, 1938. Several reports (Garlock,<sup>7</sup> Churchill and Sweet,<sup>8</sup> Carter, Stevenson and Abbott,<sup>9</sup>



Fig. 1 (case 6).—Roentgenogram taken five years after transthoracic resection of the lower part of the esophagus and the proximal portion of the stomach and esophagogastrostomy for carcinoma primary in the cardiac end of the esophagus.

6. Ochsner, A., and De Bakey, M.: *Surgical Aspects of Carcinoma of the Esophagus*, J. Thoracic Surg. **10**:401, 1941.

7. Garlock, J. H.: *The Problem of Carcinoma of the Cardiac End of the Stomach*, Surg., Gynec. & Obst. **73**:244, 1941.

8. Churchill, E. D., and Sweet, R. H.: *Transthoracic Resection of Tumors of the Stomach and Esophagus*, Ann. Surg. **115**:897, 1942; **116**:566, 1942.

9. Carter, B. N.; Stevenson, J., and Abbott, A. O.: *Transpleural Esophagogastrostomy for Carcinoma of the Esophagus and Cardiac Portion of Stomach*, Surgery **8**:587, 1940.

Jonas,<sup>10</sup> Walters,<sup>11</sup> Wu and Loucks,<sup>12</sup> W. E. Adams,<sup>13</sup> Phemister,<sup>14</sup> Stephens,<sup>15</sup> Brock<sup>16</sup>) have recently appeared of resections and anastomoses for both terminal esophageal and proximal gastric cancer, and the procedure is beginning to be extensively employed. The results have been variable, and some of these reports consist of data on 1 or 2 successful operations. No doubt many unsuccessful and successful operations have not been reported by others. In the hands of the more experienced operators the results have compared favorably with those of partial and total gastrectomies performed by the abdominal route. Many cases are included in which resection and anastomosis could not have been performed by that route except by also opening the chest after the method of Ohsawa.

The report of Churchill and Sweet<sup>7</sup> is the most outstanding, since it presents the largest published series of cases with the lowest operative mortality and contributes many valuable points to various aspects of the field. They had 13 cases of transthoracic resection and anastomosis. In 8 cases the cancer was primary in the cardiac end of the stomach and resection and anastomosis of the end of the esophagus into the anterior wall of the stomach resulted in 1 operative death. In 3 cases a similar procedure was done for a tumor primary in the lower part of the esophagus, and all the patients survived the operation. In 2 cases a total gastrectomy with esophagojejunostomy was done, and both patients died. Of the 10 patients surviving operation, 2 died of recurrence and the remainder were well and free of symptoms from three months to two and a half years after operation.

Garlock in a recent personal communication stated that he had operated on 51 patients with carcinoma of the cardiac end of the stomach. Twenty-two of the tumors were operable and were resected transthoracically with intrathoracic esophagogastronomy; there were 9 postoperative deaths. Of the 13 survivors, 4 died of recurrence in from seven to thirteen months and 9 were alive and well for periods of one month to two and a half years after operation.

While the surgical treatment of cancer of this region is still in the developmental stage, it is safe to state that transthoracic resection is the operation of choice when there is obstruction of the esophageal outlet, whether the tumor is primary in the stomach or in the esophagus. But in view of the favorable results that are being obtained with total gastrectomy by the abdominal route, there is a question as to whether the abdominal or the transthoracic route should be employed for cancer of the cardiac end of the stomach which does not obstruct the esophagus. Further experience will be necessary in order to settle the point.

#### PREOPERATIVE MANAGEMENT

Since most patients with cancer of the cardiac end of the stomach are first seen in a reduced state of nutrition, it is necessary that they receive appropriate pre-

10. Jonas, A. F.: Transpleural Esophagogastronomy: Report of a Successful Case. *Arch. Surg.* **44**:556 (March) 1942.
11. Walters, W.: Transthoracic Resection of Stomach and Esophagus for Carcinoma. *Proc. Staff Meet., Mayo Clin.* **17**:241, 1942.
12. Wu, Y. K., and Loucks, H. H.: Resection of the Esophagus for Carcinoma. *J. Thoracic Surg.* **11**:516, 1942.
13. Adams, W. E.: Recent Progress in the Surgical Treatment of Carcinoma of the Esophagus, *Surg., Gynec. & Obst.* **72**:312, 1941.
14. Phemister, D. B.: Experiences with Eight Cases of Resection of the Esophagus for Carcinoma, *J. Thoracic Surg.* **11**:484, 1942.
15. Stephens, H. B.: Cancer of the Thoracic Esophagus and Upper End of the Stomach: A Review of Twenty-three Cases That Have Undergone Surgical Exploration. *J. Thoracic Surg.* **11**:469, 1942.
16. Brock, C. R.: Cardio-Esophageal Resection for Tumor of the Cardia. *Brit. J. Surg.* **30**:146, 1942.

operative management. Rarely should an attempt be made to restore the lost weight by jejunostomy feeding, since the gain is offset by the valuable time lost. By far the most important step is the treatment of the anemia which is usually present by the transfusion of adequate amounts of blood. A high caloric diet should be given during this period. Intravenous injections of saline and dextrose solutions may also be indicated if the patient is dehydrated. Therapy with sulfonamide compounds has been started preoperatively by some and not by others, and there is insufficient evidence from which to draw conclusions as to its value.

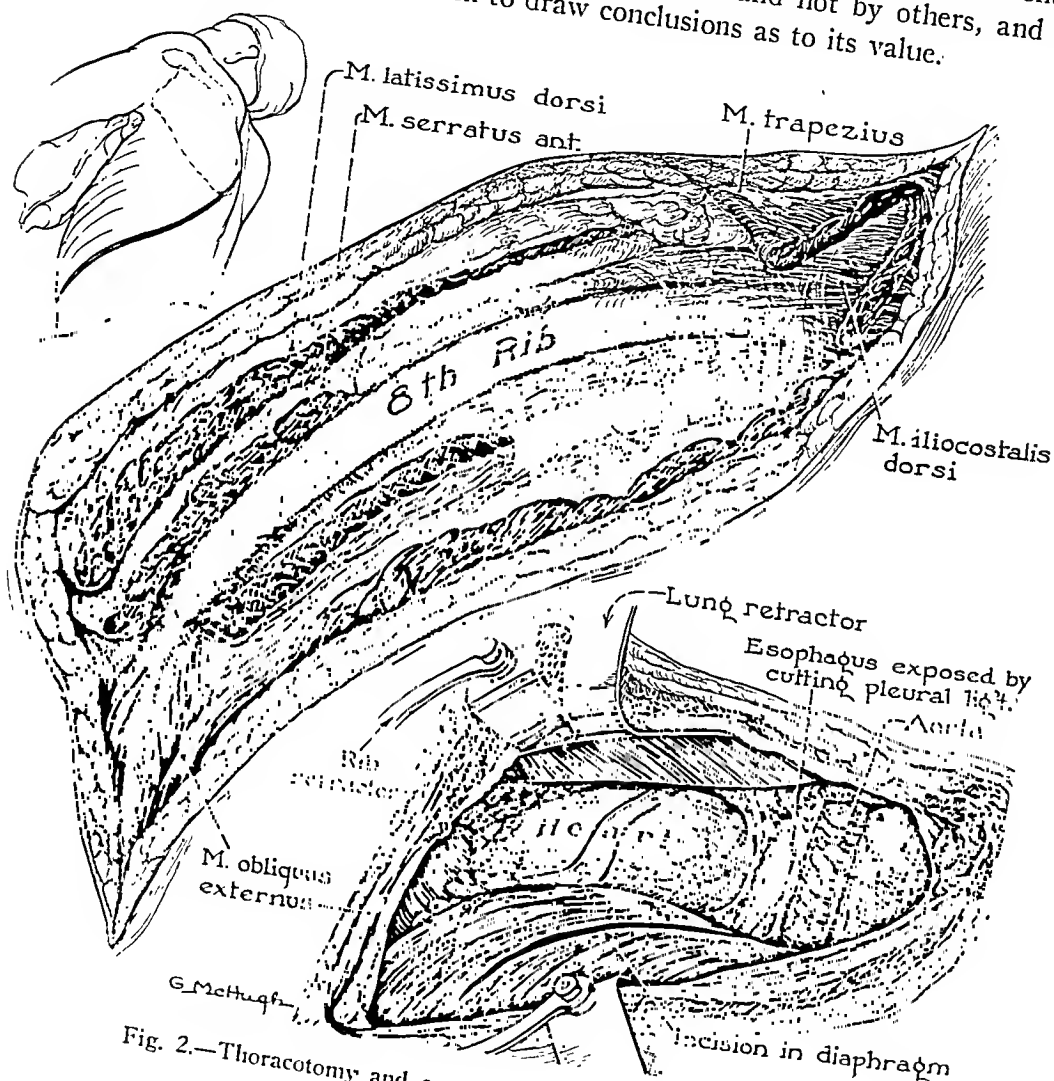


Fig. 2.—Thoracotomy and exposure of field of operation.

#### OPERATIVE TECHNIC

If the transthoracic approach is decided on, a preliminary exploratory laparotomy for the determination of operability is rarely employed. Exploration can be carried out as well through a thoracic as through an abdominal incision, and in some cases better, and although the operation is longer the patients whose cancers have proved to be inoperable have tolerated it relatively well. Also gastrostomy or jejunostomy as a palliative measure for an inoperable growth yields altogether such poor results that it is rarely advised.

My routine is to employ ethylene anesthesia with the maintenance of a positive pressure of 4 to 6 mm. of mercury by means of the face mask. A small amount of ether may be added to the gas mixture in order to permit reduction of the concentration of ethylene and increase in the oxygen concentration to around 20 per cent. Cyclopropane and oxygen and ether given with and without the intratracheal catheter have been used by others with satisfaction. Intravenous administration of physiologic solution of sodium chloride is started at the beginning, and from 600 to 1,200 cc. of blood is usually administered in the course of the operation.

The patient lies on the right side. The left arm is held vertically with the forearm flexed at a right angle and attached to an overhead rectangular frame across the table, which also supports the drapes. The left side of the chest, the left flank and the left side of the abdomen to well past the midline are painted with iodine and the field draped. An oblique incision is made over the eighth rib from the costochondral junction to the angle posteriorly and the skin surfaces walled off with towels. The overlying fibers of the latissimus dorsi, serratus anterior and trapezius muscles are then incised and the eighth rib exposed (fig. 2). The longitudinally



Fig. 3.—Hemidiaphragm-shaped lung retractor. A variation suitable in some cases has a curved portion excised at the anterior end of the mesial border (X) to avoid pressure on the heart.

coursing iliocostal muscles are freed and retracted mesially, exposing the angle of the rib. The periosteum is then incised and stripped and the rib resected from its junction with the cartilage to beyond the angle. Churchill and Sweet resect the ninth rib instead. The pleura is opened, the margins of the incision covered with laparotomy pads and an automatic rib retractor introduced. Adhesions between parietal and visceral pleural surfaces may first require division. The ligament attaching the lower lobe of the lung to the mediastinum is then divided. The esophagus, mediastinum and lung are examined for the presence of tumor. In some cases the diaphragm has been found infiltrated with tumor, a contraindication to any further attempt at resection. If no evidence of intrathoracic involvement, except of the terminal portion of the esophagus, is found, the lung is then held upward by a malleable retractor, the blade of which is shaped roughly to fit a cross section of the chest at this level (figs. 2 and 3). The retractor is covered with stockinet or with a stocking, the foot being fitted over the blade; it usually main-

tains lung retraction so well that further adjustment during the operation is unnecessary. The phrenic nerve is then pinched with a hemostat until the left half of the diaphragm is paralyzed. The diaphragm is then opened widely by means of an incision beginning near its attachment to the chest wall anterolaterally and directed toward the hiatus of the esophagus. As the hiatus is approached, branches of the left phrenic artery are encountered, which are clamped and tied. The stomach and terminal portion of the esophagus are then explored, and the extent of involvement by tumor is determined. The lymph nodes of the lesser curvature are examined for metastases. The lesser peritoneal cavity is opened by division of the attachment of the fundus to the diaphragm and its peritoneal lining and the retroperitoneal tissues explored for the presence of adhesions and metastases. The

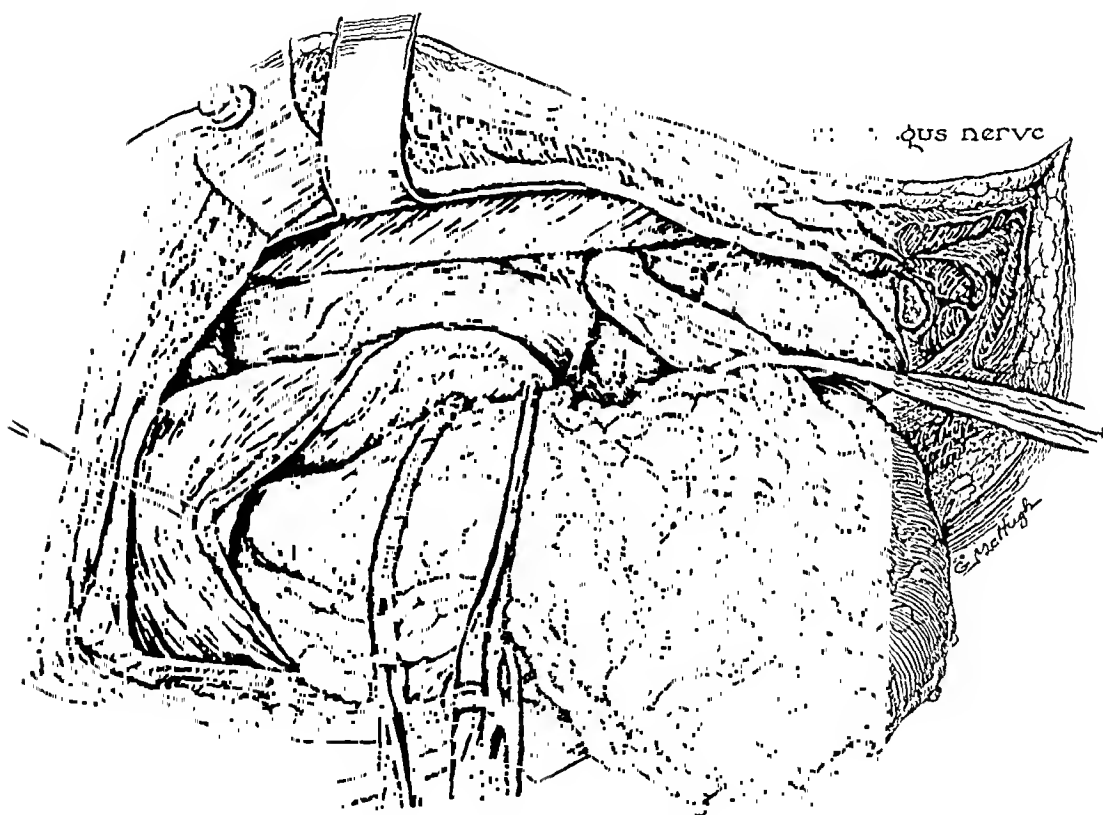


Fig. 4.—Exposure of resection.

hand is introduced into the abdomen, and a general exploration for spread of cancer is easily carried out. In some cases it is possible to judge better about operability of the lesion high in the abdomen by this approach than by an abdominal one.

If the lesion is found to be operable, the diaphragm is then opened to the esophagus. The mediastinal pleura is incised and reflected from the esophagus for a distance usually of 3 or 4 inches (8 or 10 cm.) upward, the esophagus is separated all around and a piece of umbilical tape passed about it. The separation from the diaphragm is then completed. The fundus and greater curvature are then ligated off. In the majority of cases it is preferable to remove the spleen, as the stomach then becomes more accessible.

If the spleen is found adherent to the stomach, the two structures should be taken out together. In 1 case the tail of the pancreas was also adherent and had to

be resected. If the lesser peritoneal cavity is obliterated above the level of the pancreas from extension and adhesions of the tumor posteriorly, the posterior parietal peritoneum should be dissected off and removed with the stomach, down to the pancreas. This is more easily done by the thoracic than by the abdominal approach. Division of the gastrohepatic omentum with removal of the lymph nodes of the lesser curvature and isolation and division of the left gastric artery are usually rendered easier if the greater curvature has first been freed. The freeing of the curvatures is carried well below the level of involvement when the cancer is primary in the cardiac end of the stomach; when the cardiac end of the esophagus is primarily involved the left gastric artery is always divided and ligated regardless of whether or not the stomach has been invaded, since satisfactory resection and esophagogas-

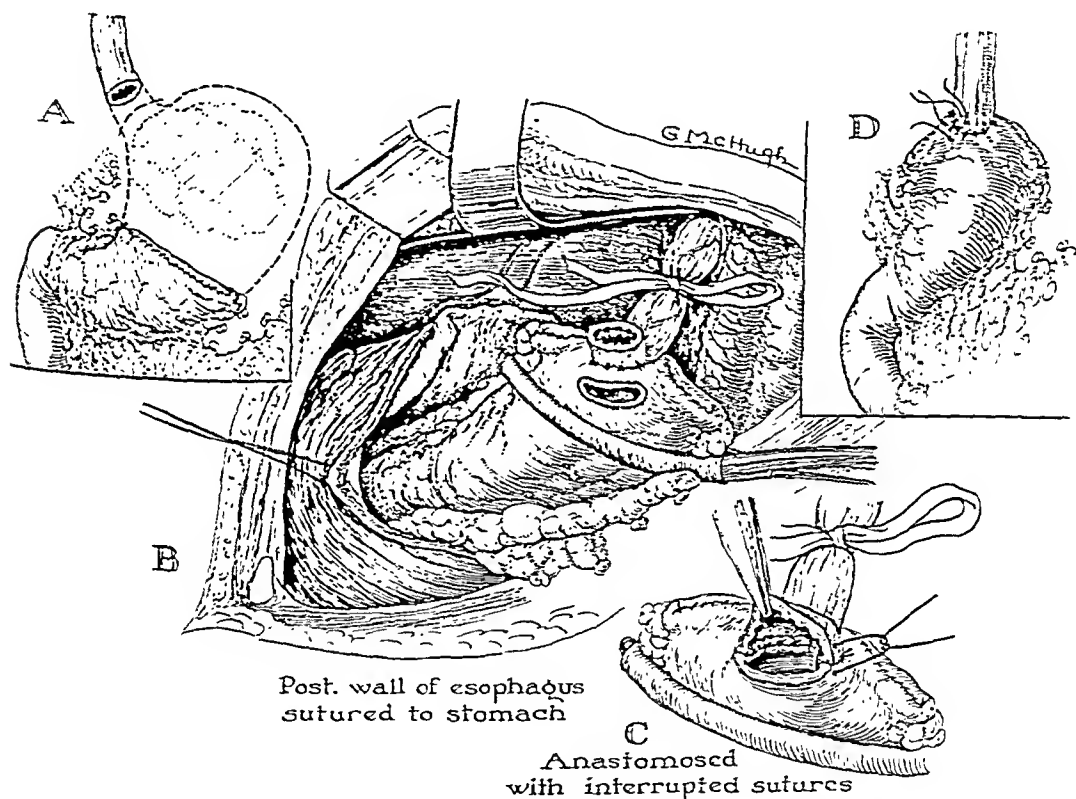


Fig. 5.—Technic of anastomosis.

trostomy are not otherwise possible. In 1 case of esophageal cardiac carcinoma, the tip of the left lobe of the liver was adherent and was resected. The tumor had extended posteriorly to the right of the aorta, and in liberating it a vessel that was thought to be thoracic duct was divided and tied.

The esophagus and stomach are then pulled forward in the chest and the resection commenced (fig. 4). An intestinal clamp is applied distally and a Payer crushing clamp proximally, and after walling off the stomach is divided just beyond it. A sucker is in readiness if fluid content is encountered. A gauze covering is tied over the proximal end with a heavy silk ligature. The distal end is then closed with linen, silk or cotton sutures, according to individual preference. The umbilical tape about the esophagus is shifted to a point about  $1\frac{1}{2}$  inches (4 cm.) above the level of division and tied twice, the second tie being a slip knot. An intestinal



clamp is used instead by most authors. The stump of stomach is then brought up into the chest to determine whether or not anastomosis may be made without undue tension. This is usually possible if one fourth or more of the stomach is left. If difficulty is experienced in approximation, it may be overcome by mobilization of the duodenum following the Kocher technic of incising the peritoneum along its right margin. The procedure was successful in 1 of the cases of this series.

A clamp is applied across the stomach to prevent leakage, and the field is walled off. In my cases, the anastomosis has been made between an opening in the anterior wall of the stomach  $\frac{3}{4}$  to 1 inch (2 to 2.5 cm.) away from the closed proximal end. An inner row of interrupted through and through and an outer row of interrupted Lembert sutures of fine linen are used (fig. 5). Mattress sutures have recently been used in 3 cases. The esophagus may be divided first, or the posterior row of Lembert sutures may be placed before division. The knots of the inner row are

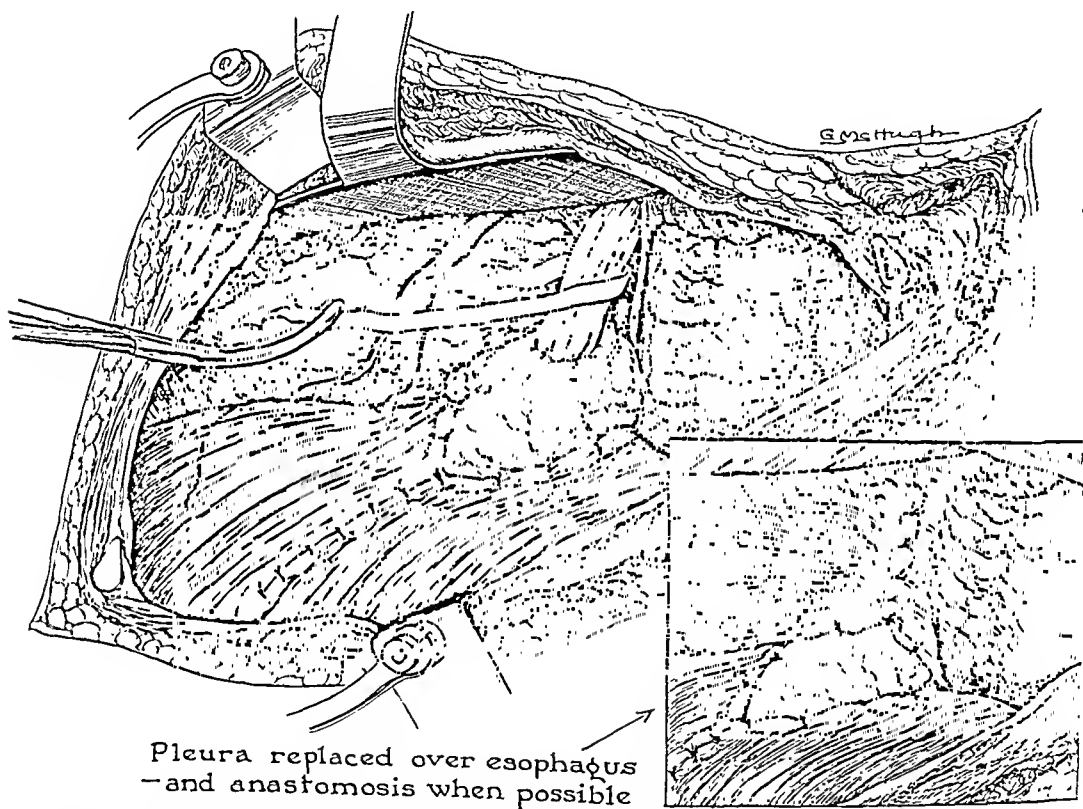


Fig. 6.—Closure of diaphragm and suture of the mediastinal pleura over the esophagus and anastomosis. When pleura is not available, omentum may be used about the anastomosis.

placed within the lumen. The sucker is usually introduced into the stomach immediately on incising the wall. In 1 case in which this was not done, there was soiling and subsequently infection and leakage of the anastomosis, with a fatal termination.

In case of inability to approximate satisfactorily the remaining portions of the stomach and esophagus, anastomosis between a loop of jejunum and the esophagus should be made. In a case of very extensive gastric resection transthoracically, Dr. Lester Dragstedt recently anastomosed the open end of the antrum with the esophagus with success.

If there is any degree of tension on the anastomosis, it may be relieved by stitching the stomach to the posterior mediastinal tissue or pleura above. However, when there is no tension this is not necessary. The mediastinal pleura is then sutured over the esophagus, and in most cases it can be made to cover the anastomosis, as shown in figure 6. If this cannot be done, the anastomosis may be surrounded by a fold of omentum sutured about it on either side, as advocated by Churchill and Sweet<sup>8</sup> as a routine procedure. These authors employ a different technic of anastomosis from the one here described which has given excellent results. Mucosa is sutured to mucosa with mattress sutures of silk, and an outer layer of the same sutures is inserted in the muscular layers of the esophagus and the muscular and peritoneal layers of the stomach. In 4 of my cases sulfathiazole was implanted about the anastomosis, with 3 survivals.

A mushroom catheter is inserted posterolaterally through the ninth interspace for pleural drainage, and the chest opening is sutured tightly. The remaining air is then sucked out of the chest and the catheter clamped until it has been attached with the tube for underwater suction drainage in the patient's room. Some authors, including Churchill and Sweet, have dispensed with drainage of the chest.

Postoperatively, the patient is placed in an oxygen tent for two to several days, depending on the course. If the progress is favorable, oxygen may be given by nasal catheter after two or three days. Sulfathiazole has been given postoperatively to 6 patients, 3 of whom died. There has been no instance of shock postoperatively. The absence of shock is attributable to the fact that any loss of blood during operation was compensated for by simultaneous blood transfusion. Any sign of peripheral circulatory embarrassment or anemia developing postoperatively was promptly treated by blood or plasma transfusion.

#### CLINICAL EXPERIENCES

In all, 10 patients with carcinoma of the cardiac region, 7 with a tumor primary in the gastric cardia and obstructing the esophagus and 3 with the primary lesion in the esophageal cardia with extension to the adjacent portion of the stomach, have been treated by transthoracic resection and esophagogastrostomy. Patients having resection and anastomosis with carcinomas located higher in the esophagus are excluded. There were 4 postoperative deaths. One patient with esophageal cancer died of auricular flutter and beginning pneumonia on the fourth day, and 1 with gastric cancer and another with esophageal cancer died of regional infection and leakage of the anastomosis on the seventh day. A third patient, with gastric cancer, made an immediate recovery from the operation and went home after three weeks. He returned six weeks after operation with a cough and low grade fever, and on examination he was found to have a small collection of pus about the anastomotic site. It was drained and after improvement he again went home; he soon returned, however with a fistulous communication with the greater curvature end of the resected stomach, a regional pulmonary abscess and a retroperitoneal abscess which migrated downward to the right inguinal region. Although the abscesses were drained, he died three and one-half months after the original operation. The first patient with cancer of the esophageal cardia who survived the operation was mentioned earlier in this paper as being free from signs of recurrence at the time of writing over five years after operation. Of the 5 patients with primary gastric cancer who survived the operation, 1 was found dead in the bathroom three months after operation and the cause of death was not learned; 1 died of recurrence one and one-half years after operation; 1 is alive and apparently free from recurrence one year and eight months after operation; 1 is

well two months after operation and 1 was operated on only one month prior to the time of writing. In addition, 5 patients have been subjected to transthoracic exploration and 3 to abdominal exploration, and all proved to have inoperable cancer. All recovered from the operation except 1 patient subjected to transthoracic exploration, who died on the sixth day, of pulmonary embolism.

#### REPORT OF CASES

##### *Cancers Primary in the Cardiac End of the Stomach with Esophageal Obstruction.*

CASE 1.—A man aged 46 years complained of gradually increasing difficulty and pain on swallowing and loss of 25 pounds (11.3 Kg.) over a period of thirteen months. Roentgenologically there were narrowing of the esophageal cardia and a large filling defect in the



Fig. 7 (case 3).—Carcinoma of the cardiac end of the stomach.

proximal third of the stomach. At operation a large carcinoma of the proximal half of the stomach obstructing the end of the esophagus was found. The spleen and the tail of the pancreas were adherent to the gastric tumor. The proximal two thirds of the stomach, the distal  $1\frac{3}{4}$  inches (4.5 cm.) of the esophagus, the spleen and the tail of the pancreas were removed in one mass by transthoracic and transdiaphragmatic resection, and esophagogastrostomy was done. Recovery was uneventful. Microscopic examination of the resected tissue revealed scirrhous carcinoma of the stomach with metastases to the lymph nodes of the lesser curvature. Symptoms of recurrence appeared after ten months, and after eighteen months the patient died.

CASE 2.—A man aged 62 years complained of loss of 35 pounds (16 Kg.) and "stomach trouble" for nine months and difficulty in swallowing for four months. Roentgenologically there were narrowing of the esophageal outlet and evidence of a polypoid mass in the fundus and the cardiac end of the stomach. At operation it was found that the tumor involved the

lesser curvature and the posterior wall of the stomach and the end of the esophagus. There were no metastases to lymph nodes. The spleen was adherent to the tumor. Transthoracic resection of the proximal two thirds of the stomach and 1 to 1½ inches (2.5 to 4 cm.) of esophagus, splenectomy and esophagogastrostomy were done. There was seiling from the stomach during the performance of the anastomosis. Microscopic examination revealed adenocarcinoma. The patient died in seven days from leakage of anastomosis and empyema of the left side of the chest.

CASE 3.—A man aged 56 years had lost 15 pounds (7 Kg.) in a year and had noticed fulness in the epigastrium after meals and increasing difficulty in swallowing for six months. Roentgenologic examination revealed narrowing of the terminal esophagus and a filling defect of the cardiac end of the stomach (fig. 7). Transthoracic and transdiaphragmatic exploration revealed a large tumor mass in the cardiac region and the posterior wall of the stomach with extension to the end of the stomach. There were metastases in the lymph nodes of the lesser



Fig. 8 (case 3).—Appearance following resection and esophagogastrostomy.

curvature. Partial gastrectomy from the middle of the greater curvature to the lower one third of the lesser curvature including lymph nodes, removal of the lower 2 inches (5 cm.) of the esophagus and esophagogastrostomy were done. Microscopic examination of the tumor proved it to be adenocarcinoma. Convalescence was uneventful except for a superficial infection in the front end of the incision in the chest. The patient has remained free from signs of recurrence for one year and eight months and is active but somewhat undernourished. Figure 8 shows the postoperative roentgenologic appearance.

CASE 4.—A man aged 52 years had suffered from loss of appetite and epigastric distress for three months and from difficulty in swallowing for six weeks. He had lost 35 pounds (16 Kg.). Roentgenologic examination revealed narrowing of the terminal portion of the esophagus and a large, irregular filling defect of the proximal portion of the stomach extending along the lesser curvature. Transthoracic exploration revealed a very large tumor at the cardia and extending along more than half of the lesser curvature, with metastases to lymph nodes and infiltration of the end of the esophagus. Splenectomy, resection of the proximal three fourths of stomach and 2 inches (5 cm.) of the esophagus, Kocher mobilization of the

duodenum and esophagogastrostomy were done. Omentum was sutured about the anastomosis. Sulfathiazole therapy was employed for six days. Convalescence was uneventful for three weeks, and the patient went home. A local empyema pocket, which communicated with the resected end of the stomach, was drained in six weeks. A pulmonary abscess and a retroperitoneal abscess which dissected to the right inguinal region were also drained. After three and a half months the patient died. Perhaps too much of the greater curvature was saved, since there was a long narrow tube of stomach, the end of which became the seat of an abscess with latent leakage.

CASE 5.—A man aged 64 years lost 70 pounds (16 Kg.) in a few months. He suffered from difficulty in swallowing and pain in the epigastrium and the back for two months. Roentgenologic examination showed a large filling defect in the fundus of the stomach and a narrowing of the cardia. Transthoracic exploration revealed a hard tumor in the fundus and the cardia of the stomach and the intrathoracic portion of the esophagus. There were no metastases. Splenectomy, resection of the proximal two thirds of the stomach and  $2\frac{1}{2}$  inches (6 cm.) of the esophagus and esophagogastrostomy were done. Microscopic examination of the tumor showed it to be adenocarcinoma of the stomach. Postoperative convalescence was uneventful, but the patient remained in a rather poor nutritional state. There were no obstructive symptoms. He was found dead in the bathroom three months later. The cause of death was not learned.

CASE 6.—A man aged 82 years, weighing 205 pounds (93 Kg.) and well preserved, had increasing difficulty in swallowing for one month. Roentgen examination revealed irregular narrowing of the terminal portion of the esophagus and a filling defect in the proximal portion of the stomach. Transthoracic and transdiaphragmatic exploration revealed a large, hard mass in the terminal  $1\frac{1}{2}$  inches (4 cm.) of the esophagus and the proximal end of the stomach with large metastases to the lymph nodes on the lesser curvature near the left gastric artery. At operation splenectomy, resection of the proximal third of the stomach, the enlarged lymph nodes and the terminal 3 inches of the esophagus and esophagogastrostomy were performed. Sulfathiazole was given preoperatively and postoperatively and was implanted about the anastomosis at operation. Microscopic examination revealed a columnar cell carcinoma of the stomach, secondarily involving the esophagus. Convalescence was uneventful. The patient left the hospital in three weeks and was free from gastroesophageal symptoms two months after operation.

CASE 7.—A man aged 51 years had increasing difficulty in swallowing over a period of seven months and pains in the left upper quadrant of the abdomen and lower part of the chest for three months associated with a loss of 20 pounds (9 Kg.) in weight. Roentgenologic examination revealed a definitely obstructive lesion of the lower end of the esophagus and a filling defect of the first part of the lesser curvature of the stomach. Transthoracic and transdiaphragmatic exploration revealed a hard nodular tumor of the proximal end of the stomach involving the terminal portion of the esophagus and several enlarged lymph nodes about the left gastric artery and retroperitoneally above the pancreas. At operation splenectomy, removal of the peritoneal walls of the lesser peritoneal cavity and resection of the proximal two thirds of the stomach, including the lesser curvature, of the lymph nodes and of the distal  $2\frac{1}{2}$  inches (6 cm.) of the esophagus, followed by esophagogastrostomy, were performed. A small nodule palpated in the right lobe of the liver may have represented a metastasis. Sulfathiazole was implanted in the wound and administered postoperatively. Microscopic examination revealed adenocarcinoma. Convalescence was uneventful for five weeks after operation.

*Cancers in Cardiac Portion of Esophagus with Extension to Stomach.*

CASE 8.—This patient was mentioned earlier in this article and has been previously reported on. A woman aged 53 years complained of difficulty in swallowing and weakness for three months. She had lost 10 pounds (4.5 Kg.). Roentgenologic examination revealed narrowing of all of the cardiac portion and about 1 inch (2.5 cm.) of the intrathoracic portion of the esophagus. Transthoracic and transdiaphragmatic exploration showed a firm tumor mass in the lower 3 inches (8 cm.) of the esophagus with slight extension into the stomach and metastases to the lymph nodes along the upper curvature. Resection of the proximal portion of the stomach and the terminal 4 inches (10 cm.) of the esophagus and esophagogastrostomy were carried out. A small catheter gastrostomy was also done. Convalescence was uneventful, and the patient was well and free from signs of recurrence five years postoperatively.

CASE 9.—A man aged 67 years had noticed weakness and loss of 40 pounds (18 Kg.) during four months. He had suffered from difficulty and pain on swallowing for three and one-half months and from aching in the lower part of the back for four months. Roentgenologic examination revealed a filling defect in the cardiac region of the stomach and narrowing of about 1 inch (2.5 cm.) of the terminal portion of the esophagus. The diagnosis was carcinoma

of the cardiac end of the stomach with secondary involvement of the esophagus. Transthoracic and transabdominal exploration revealed a tumor in the proximal end of the stomach and the terminal  $1\frac{1}{2}$  inches (4 cm.) of the esophagus adherent to the tip of the left lobe of the liver and invading tissues posteriorly at and just below the level of the diaphragm. Splenectomy, resection of the proximal half of the stomach, of the terminal three and one-half inches (9 cm.) of the esophagus and of the tip of the left lobe of the liver and esophagogastrostomy were done. During the liberation of the posterior extension of tumor what was thought to be the thoracic duct was resected and ligated. Sulfathiazole was administered postoperatively. Fibrillation developed and continued despite digitalization. The patient died on the fifth day with beginning pneumonia. Microscopic examination of the tumor showed it to be squamous cell carcinoma, primary in the esophagus, with extensive involvement of the stomach.

CASE 10.—A man aged 62 years had been known to have diabetes for one year. He had had progressive difficulty in swallowing for fifteen months and had lost 50 pounds (23 Kg.) in weight. Roentgenologic examination revealed narrowing of the lumen of the terminal 2 to 3 inches (5 to 8 cm.) of the esophagus. Esophagosopic examination and biopsy showed squamous cell carcinoma. Transthoracic and transdiaphragmatic exploration revealed a hard tumor of the terminal thoracic and the intra-abdominal portion of the esophagus and of the cardiac portion of the stomach. There were extensive metastases along the lesser curvature and retroperitoneally, with retrogastric adhesions. At operation splenectomy, resection of the proximal three fifths of the stomach, the adherent lymph nodes and posterior portion of the peritoneum and the terminal  $3\frac{1}{2}$  inches (9 cm.) of the esophagus, followed by esophagogastrostomy, were performed. The anastomosis was on tension, for relief of which the stomach was sutured to the pleura above. Symptoms of mediastinitis and of pleurisy on the right side developed on the fifth postoperative day and on the seventh day the patient died. Autopsy revealed leakage of the anastomosis.

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# TRANSTHORACIC SUBTOTAL GASTRECTOMY AND ESOPHAGECTOMY FOR CANCER

## REPORT OF A CASE

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Such radical operative procedures as esophagectomy for cancer of the esophagus and total gastrectomy for certain cancers of the stomach are now being done with increasing frequency. Numerous surgeons, both European and American (Fischer,<sup>1</sup> Sauerbruch,<sup>2</sup> Phemister,<sup>3</sup> Garlock,<sup>4</sup> Carter, Stevenson and Abbott,<sup>5</sup> Churchill,<sup>6</sup> Ochsner and DeBakey,<sup>7</sup> Jonas,<sup>8</sup> Cattell<sup>9</sup> and Marshall<sup>10</sup>), have successfully resected cancers involving both the cardiac portion of the stomach and the terminal portion of the esophagus, such operations being performed by a transthoracic, transdiaphragmatic approach and completed usually by an intrathoracic esophagogastric anastomosis.

In the patient whose case is reported here, so much of the stomach and esophagus was involved by cancer as to prohibit such an anastomosis. Consequently a subtotal gastrectomy and a subtotal esophagectomy, with subsequent construction of a prethoracic artificial esophagus, were necessary.

## REPORT OF CASE

R. B., a Russian Jew born in December 1900, applied to the Memorial Hospital for treatment on July 17, 1940. Prior to the present illness he had never been ill. His habits were exemplary. His chief complaints were epigastric pain, dysphagia, substernal discomfort, regurgitation of food and hematemesis.

*Present Illness.*—Since 1933 the patient had complained intermittently of epigastric pain, nausea and heartburn. His weight had always been maintained at 180 pounds (81.5 Kg.). Finally, in June of 1938, when 37 years of age, he vomited bright red blood and one week later was admitted to another hospital in New York city. Physical examination revealed an

From the Memorial Hospital for the Treatment of Cancer and Allied Diseases.

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apparently normal abdomen. Gastric analysis gave normal results. The hemoglobin content of the blood was 50 per cent. The stools contained blood (4 plus). Fluoroscopic and roentgenographic examination revealed a tumor occupying the cardia and the fundus. An exploratory laparotomy was performed, and a nodular tumor mass was found on the lesser curvature of the stomach extending to the level of the esophagus, so that it was deemed mechanically impossible to resect it. The abdomen was therefore closed without removal of a specimen for biopsy. The patient convalesced uneventfully but continued to experience discomfort on swallowing solid food.

*Physical Examination.*—Two years after his first admission to a hospital he was accepted at the Memorial Hospital, at which time he was still in good general health, although he had lost 10 pounds (4.5 Kg.) in weight and was moderately anemic. His physical examination at this time revealed essentially normal conditions, and the tumor in his stomach could not be palpated. There was no evidence of extension of the cancer to involve the liver, the peritoneum and the rectovesical pouch.

*Röntgen Examination.*—Fluoroscopic and roentgenographic studies revealed a bulky soft tissue mass occupying the cardiac and fundal portions of the stomach. A constricting defect involved the distal portion of the esophagus with dilatation proximal to it. It was evident that the cancer extended upward to involve the thoracic esophagus.

*Esophagoscopy.*—A rigid gastroscope was passed with the area under local anesthesia. A flat granular tumor was encountered in the terminal portion of the esophagus at a distance of 39 cm. from the upper dental arch. The clinical impression was that the tumor originated in the stomach with secondary extension into the esophagus. A biopsy specimen obtained at this time was reported as "adenocarcinoma, gastric type, grade 3."

*Laboratory Studies.*—Gastric analysis could not be done because of the degree of cardiac stenosis. The stools did not contain occult blood. The urine was normal. The blood count on July 22, 1940 was as follows: hemoglobin content, 52 per cent; erythrocytes, 2,816,000; white cells, 13,800, with a normal differential distribution. The protein content of the serum was 6.7 per cent. The sodium chloride content of the blood was 579 mg. per hundred cubic centimeters, the sugar content 132 mg. and the urea nitrogen content 12.9 mg.

*Operation, First Stage.*—Exploratory laparotomy and jejunostomy were performed Aug. 26, 1940. With the patient under spinal anesthesia induced with pontocaine hydrochloride, a left superior midrectus incision was made and the abdomen explored. The liver, peritoneum and abdominal viscera other than the stomach were clinically free from involvement by cancer. A very large gastric tumor was encountered which occupied the upper two thirds of the stomach and extended superiorly into the esophagus through the diaphragm. The lesser curvature was involved as low as the antrum. The tumor was largely intragastric and was moderately movable except for the esophageal extension. It was then decided that the cancer was resectable through the transthoracic, transdiaphragmatic approach. The first step therefore was to perform a jejunostomy for feeding purposes; this was done immediately by the Marwedel technic. The feeding catheter was then withdrawn through a separate stab wound on the left and the jejunum anchored to the abdominal wall beneath without torsion, tension or kinking. The abdominal wound was closed by through and through braided silk sutures.

A high caloric diet was given through the jejunostomy by means of a Murphy drip arrangement. Before, during and after this first stage, the patient received three blood transfusions of 600 cc. each. On one occasion he vomited a small quantity of old blood. Electrocardiographic studies were considered normal. In preparation for the second, more radical operation of resection, pneumothorax (left) was induced on five occasions, from 350 to 450 cc. of air being used.

*Operation, Second Stage.*—Transthoracic, transdiaphragmatic, subtotal resection of the stomach, lower esophagectomy and terminal esophagostomy were performed Oct. 1, 1940, with the patient under anesthesia induced by rectal administration of avertin with amylene hydrate supplemented by intratracheal nitrous oxide-oxygen-ether anesthesia. The patient was placed on his right side. A continuous transfusion was started through a vein in the right foot. A long incision was made in the seventh intercostal space, curving upward between the scapula and the upper dorsal portion of the spine. The fifth, sixth and seventh ribs were cut posteriorly and the intercostal vessels ligated. A pneumonolysis was necessary to free the collapsed lung. The left phrenic nerve was gently crushed for temporary immobilization of the left half of the diaphragm. The terminal portion of the esophagus was dissected free, and an umbilical tape was passed beneath it for purposes of traction. The diaphragm was incised from the costal attachment to the hiatus, the contents of the abdomen thus being exposed. Dissection was carried downward medially and laterally to free the cardia, fundus and lesser curvature of the stomach. The coronary vessels and the left gastroepiploic vessels were doubly ligated and severed. After the gastrocolic and gastrohepatic ligaments had been severed, the



mobilized stomach was readily pulled up into the thoracic cavity. A dePetz clamp was then applied across the stomach distal or caudal to the tumor, and the segments were severed between the hemostatic silver clips. The cut surface of the distal segment was then closed by seromuscular silk sutures. The residual stomach consisted only of the antrum and was

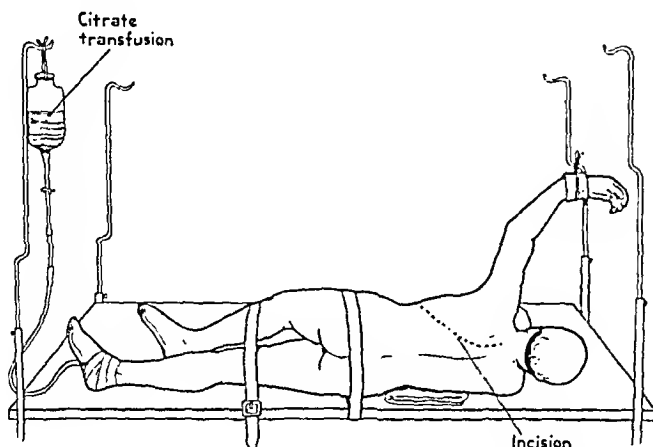


Fig. 1.—Position of patient for transthoracic, transdiaphragmatic resection of esophagogastric cancer.

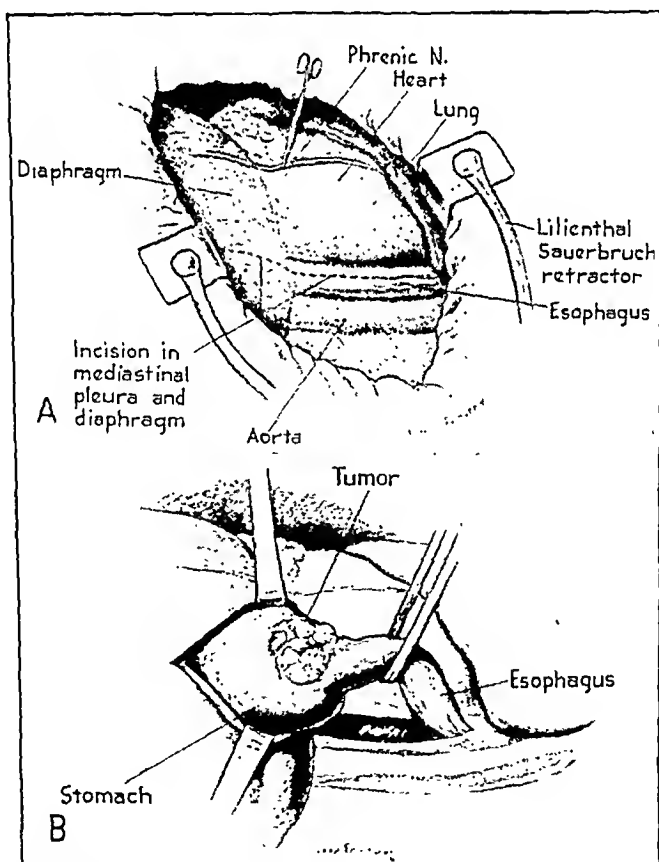


Fig. 2.—*A*, surgical exposure. A continuous incision is made through the mediastinal pleura and the diaphragm. The phrenic nerve is lightly clamped to produce temporary paresis. *B*, mobilization of the terminal portion of the esophagus and the cardia and fundus of the stomach.

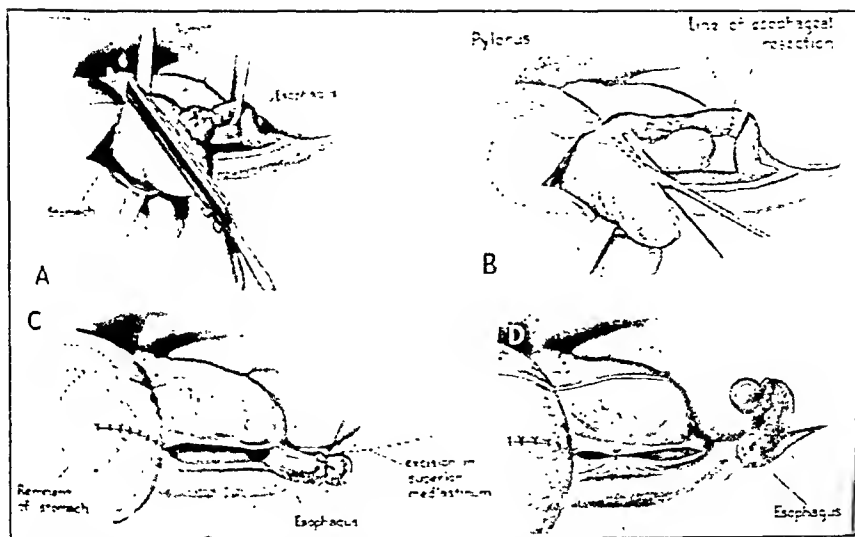


Fig. 3.—*A*, application of de Petz clamp obliquely across the stomach wall distal to the tumor. *B*, severance of proximal cancerous segment of stomach from the uninvolved distal segment. Figures 3 *A* and 3 *B* illustrate the usual technic whenever a subsequent esophago-gastric anastomosis is planned, but in the accompanying case report the cardiac and fundal cancer was so large that all of the stomach except the antral and pyloric fourth was removed. The de Petz clamp in this case extended almost to the incisura. *C*, the repaired distal gastric stump has been restored to the abdomen and the defect in the diaphragm repaired by two layers of sutures. *D*, closure of mediastinal pleura and continued mobilization of the esophageal stump in the superior portion of the mediastinum.

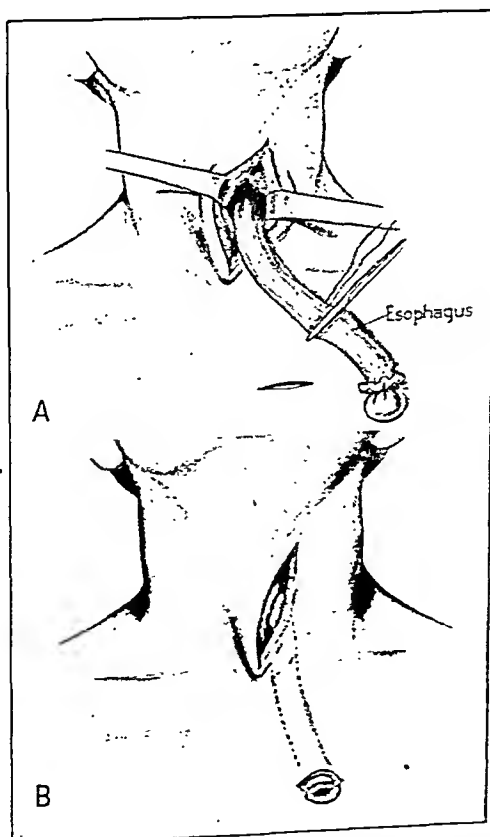


Fig. 4.—*A*, exposure of the cervical portion of the esophagus and delivery of remainder of esophagus through the neck wound. *B*, the proximal esophagus is placed in a subcutaneous tunnel in order to function as an anterior thoracic esophagostomy opening.

too small to permit a new esophagogastric anastomosis. Furthermore, the jejunal mesentery was abnormally short, and the presence of the jejunostomy militated against the establishment of an esophagojejunal anastomosis. Therefore the residual stomach was left in situ in the abdomen, and the defect in the diaphragm was closed by two layers of sutures. The tumor-bearing portion of the stomach was then lifted out of the thoracic wound, and the esophagus was freed up to the aortic arch. The esophagus above the tumor was doubly ligated with braided tape and amputated between the ligatures, the proximal stump being cauterized with phenol and alcohol. The cancerous stomach and esophagus were then removed from the field of operation. The distal end of the severed esophagus was covered by a protective ligated rubber dam. The thoracic portion of the esophagus was mobilized by tunneling upward in the esophageal bed. The esophageal arteries were clamped, cut and ligated. The parietal pleura was incised above the aortic arch and the esophagus was brought up through this opening. The defect in the parietal pleura was sutured. A stab wound was made laterally



Fig. 5.—The patient with a rubber tube connecting the esophagostomy opening and a subsequently constructed Janeway gastrostomy opening.

in the wall of the chest, and a right-angle soft rubber tube drain was placed in the left costophrenic angle and sutured in place. The chest wound was closed in layers with interrupted sutures in the usual manner, and a compression bandage was applied. With the patient on his back, an incision was made in the left side of the neck extending from the left sternoclavicular junction upward for 7 cm. along the sternomastoid muscle. The left lobe of the thyroid was retracted laterally, and the cervical portion of the esophagus was identified. The thoracic portion of the esophagus was easily withdrawn through the wound defect. A stab wound was then made in the skin of the left anterior portion of the thoracic wall, and connection with the wound in the neck was effected by blunt subcutaneous burrowing. Through this channel the esophagus was pulled to form an external esophagostomy opening. The cervical wound was then closed.

The patient was immediately placed in an oxygen tent and convalesced satisfactorily. He was removed from the oxygen tent on the fourth postoperative day and suffered no respiratory

distress. Use of the closed drainage system was discontinued on the fifth postoperative day. Three blood transfusions of 600 cc. each were given during and after this operation. The redundant esophagus protruding from the wound in the chest was removed by cauterization. The patient was able to swallow liquids without distress, and the occasional swallowing of weak solution of sodium hypochlorite was encouraged to cleanse the esophageal stoma. A roentgenogram of the chest made two weeks later revealed good expansion of the left lung and only slight residual pneumothorax.

*Pathologic Report.*—The specimen consisted of 5 cm. of esophagus and the greater part of the stomach. The bulky intragastric tumor expanded the cardia, fundus and lower part of

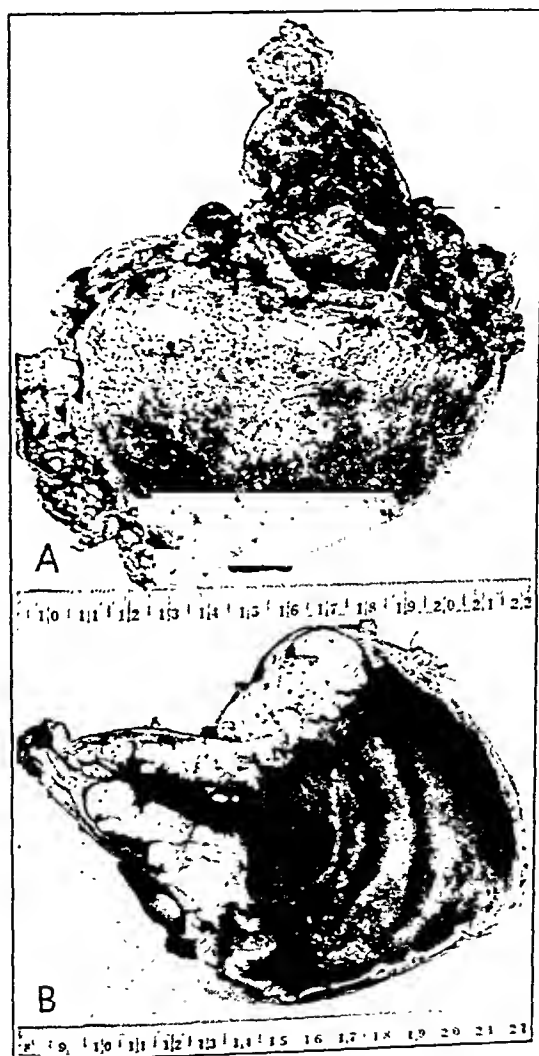


Fig. 6.—*A*, gross specimen. The degree of esophageal involvement may be seen above the level of attachment of the diaphragm. *B*, gross specimen. Sagittal section of the stomach to show the papillary character of the tumor and its protrusion into and obstruction of the terminal portion of the esophagus. One subcardiac lymph node contains metastatic carcinoma.

the esophagus; the esophagocardiac junction measured 4 cm. in diameter. Two lymph nodes along the lesser curvature adjacent to the lower part of the esophagus at the cardiac junction were found to be grossly involved by metastatic cancer; this was confirmed by subsequent microscopic study. When the stomach was sectioned, a bulky, ulcerating, exophytic papillary tumor was revealed, the cut surface of which was grayish white and granular. The neoplasm completely encircled the cardia and extended for several centimeters onto the fundus, the greater part involving the anterior surface. For the most part the tumor was relatively non-

infiltrative, but there was deep penetration of the muscularis at the beginning of the lower curvature and at the junction of the esophagus and the cardia. The neoplasm extended up the mucosa and wall of the esophagus for a distance of 3 cm.; the bulk of the intracavitary tumor, however, was represented by a blunt, unattached papillary protrusion from the main body of the tumor. There were no mucosal polyps.

Microscopic study of the tumor by Dr. Frank Koester led to the diagnosis of adenocarcinoma, grade 3, with metastasis to two perigastric lymph nodes. The structure of the cancer varied from portions of rather orderly glandular adenoma malignum, grades 1 and 2, to other portions which were nearly solid adenocarcinoma, grade 3. In one lymph node the metastatic

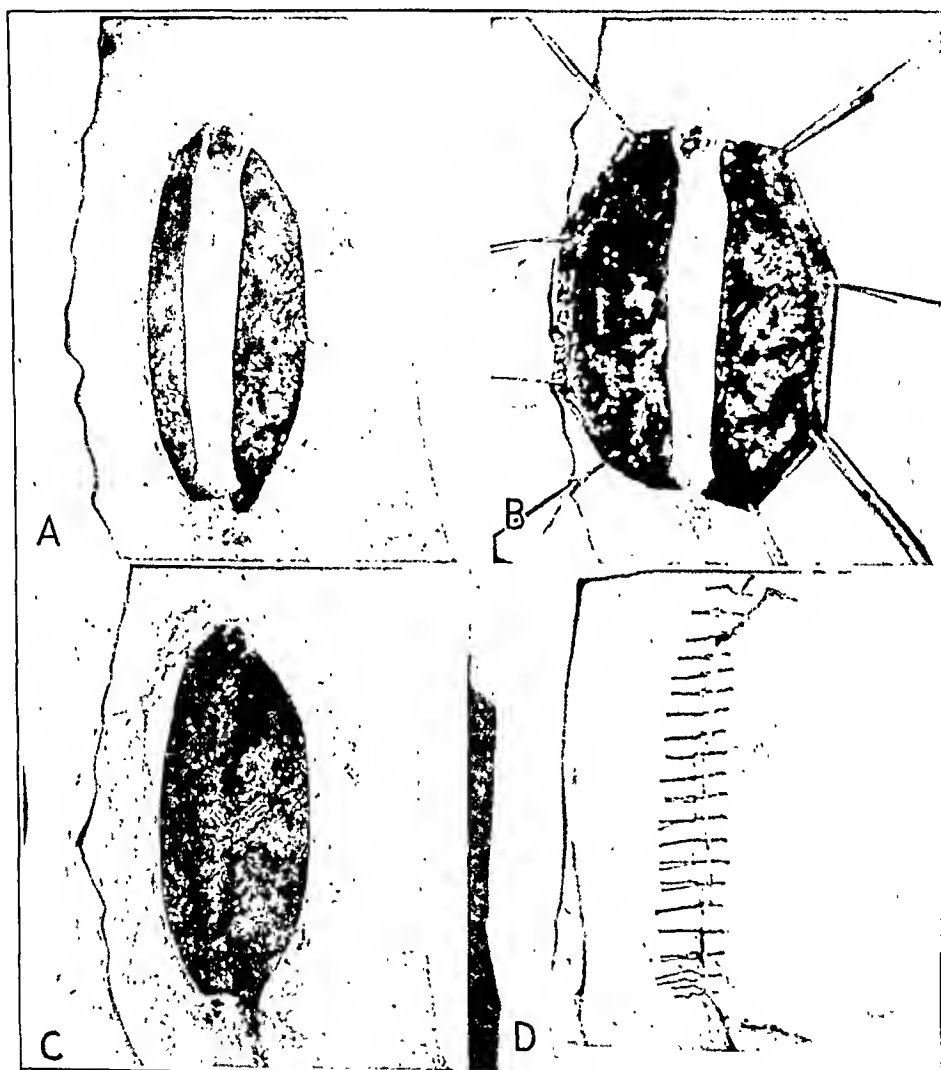


Fig. 7.—*A*, first step in prethoracic dermatoesophagoplasty. The central strip of skin is unmolested posteriorly. *B*, second step in dermatoesophagoplasty. The lateral margins are dissected widely back in order to approximate their edges later over the constructed tube of skin. *C*, the tube of skin has been constructed. *D*, the lateral flaps of skin may be sutured without great tension over the new esophagus.

tumor was adenoma malignum, and in the second node it was adenocarcinoma. The gastric mucosa was apparently normal in its microscopic aspects.

*Operation, Third Stage.*—A Janeway gastrostomy was performed Oct. 24, 1940. With the patient under spinal anesthesia induced with pontocaine hydrochloride, an upper left midrectus incision was made and the distal stump of the stomach freed from its many adhesions. The cubic capacity of this residual stomach was only 200 cc. Hence the construction of a gastrostomy fistula was difficult. A flap of anterior gastric wall, measuring 2.5 cm. in width and

7 cm. in length, was developed with its pedicle end coming off the greater curvature. The flap margins were then approximated by two rows of sutures in the conventional manner to construct the mucosa-lined tube or goose-neck which characterizes the Janeway gastrostomy.

A transfusion of 500 cc. of blood was given during the operation. A rubber catheter through the gastrostomy and through the pylorus into the duodenum was used for feeding. As soon as this functioned satisfactorily, i.e., when a liquid diet furnishing 3,000 calories could be given, the jejunostomy catheter was removed, and this wound was permitted to heal spontaneously. Considerable colicky pain accompanied each feeding. This was relieved by dilatation of the pylorus through a small gastroscope introduced via the gastrostomy and by intermittent hydrostatic (balloon) dilatation of the tiny stomach until its capacity increased to 450 cc. Fluoroscopic examination after barium was introduced through the gastrostomy showed no evidence of obstruction in the stomach, the duodenum or the jejunum. The patient received liver parenterally and supplementary vitamins. The weight remained unchanged at 135 pounds (61.2 Kg.).

*Operation, Fourth Stage.*—Anterior or prethoracic dermatoesophagoplasty was performed April 18, 1941. Although it was possible to connect the esophagostomy and gastrostomy stomas by means of an intercommunicating rubber tube, swallowing by this arrangement was not completely satisfactory because of discomfort and leakage. The esophagostomy opening was between the second and the third rib on the left side, approximately 1 cm. to the left of the sternal margin. With the patient under ether inhalation anesthesia, parallel skin incisions 2 inches (5 cm.) apart were made, extending from the esophagostomy to the gastrostomy stoma. The two inner edges were then rolled together and sutured in two layers without molesting the broad underlying base. This made a skin-lined tube. The lateral flaps of the original incisions were then widely undercut in order to mobilize them and permit their approximation over the tube just constructed. This closure was effected by vertical interrupted mattress sutures of black silk. The incisions were narrowed in the upper portion and brought above the level of the esophagostomy orifice, so that this closure made the proper communication between the original and the artificial esophagus. The lower communication with the gastrostomy stoma was not closed at this time.

*Subsequent Course.*—There was some wound infection, which was readily controlled. The patient convalesced satisfactorily and was in good health when he was discharged to his home. On July 8, 1941, three months after the last operation, he became despondent and jumped out of a third story window. He died the same day of shock and internal hemorrhage.

Postmortem examination showed multiple fractures of the bony pelvis with rupture of the urinary bladder and the pelvic colon. The mediastinum was healed, although a sterile pocket of fibrin was found in one part of the esophageal bed. One small aortic lymph node was found to contain metastatic carcinoma.

#### SUMMARY

There are several interesting features about the case reported.

1. There was a history of indigestion, dysphagia and other symptoms of gastric cancer starting in a young man, of 33 years. These symptoms continued for five years before the cancer was discovered by roentgenography and laparotomy.
2. At the age of 38 years the patient was subjected to an initial exploratory operation at another hospital, at which time the size and location of the tumor at the cardia were such as to cause the lesion to be classified as inoperable by abdominal approach.
3. Two years later it was still possible to resect this cancer by using a trans-thoracic and transdiaphragmatic approach.
4. Because the cancer involved the major part of the stomach (superior two thirds) and a considerable segment of the esophagus as well, it was not possible to accomplish an intrathoracic anastomosis of the esophagus either to the residual stomach or to the jejunum.
5. The operative procedures required four stages: (1) abdominal exploration to ascertain the extent of the disease and temporary jejunostomy for feeding purposes, (2) transthoracic and transdiaphragmatic subtotal resection of the stomach and esophagus with permanent anterior esophagostomy, (3) construction of a

permanent gastric fistula by a Janeway gastrostomy and (4) anterior or prethoracic dermatoesophagoplasty to unite the esophagostomy stoma and the gastrostomy stoma.

6. The pathologic specimen showed that the bulk of the tumor was a papillary intragastric adenoma malignum of low grade malignancy, which could account for the long history, slow rate of growth and failure of the cancer to metastasize widely. In two regions, however, the cancer had become solid adenocarcinoma, grade 3.

7. The arduous effort and expenditure of time by numerous members of the hospital staff and the great expense borne by the hospital during the eight months of care came to naught when the patient, in a moment of despondency, committed suicide. The discovery at autopsy of a single tiny preaortic lymph node containing one focus of metastatic carcinoma made the heroic sequence of major operations seem futile.

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# PROGNOSIS AND END RESULTS IN THE TREATMENT OF CANCER OF THE STOMACH

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The only hope of cure for carcinoma of the stomach at present resides in establishing the diagnosis at a time when surgical removal of the growth is possible. The main opportunity to reduce the great number of deaths which this condition causes annually (38,000 for the United States of America) lies in establishing the diagnosis earlier in a greater proportion of cases, so that more patients may be afforded the possible benefits of gastric resection.

As has been emphasized by Livingston and Pack,<sup>1</sup> any consideration of ultimate results obtained in the treatment of gastric carcinoma should take into account first the entire number of cases in which the diagnosis has been established and subsequently determine how many of the patients have been cured. Those who may be interested in a detailed statistical study of carcinoma of the stomach are referred to a work based on our experience in the Mayo Clinic.<sup>2</sup>

From 1907 to 1938 inclusive, the diagnosis of carcinoma of the stomach was made at the Mayo Clinic in 10,890 cases. Of these, the lesions in 4,648 (42.7 per cent) were considered to be inoperable, and the patients received only palliative medical treatment. The remaining 6,242 (57.3 per cent) patients underwent exploratory operation in the hope that gastric resection might be accomplished. Among this group, inoperable lesions were found in 2,431 cases (22.3 per cent of the entire series of 10,890 cases), and in each case the incision was closed and nothing further was done. In an additional group of 1,039 cases (9.5 per cent of the original series of 10,890 cases) the lesion could not be removed but some form of palliative procedure appeared to be worth while and was performed. In 2,772 (25.5 per cent) of the original 10,890 cases in which the diagnosis was established, gastric resection actually was accomplished. Thus, approximately 1 of 4 persons whose condition was diagnosed as gastric carcinoma during these years had the lesions removed surgically and thereby, provided they survived the operation, had some chance of ultimate cure.

In this series, then, the surgical rate of gastric carcinoma averaged 57.3 per cent and the resectability rate (calculated on all patients) was 25.5 per cent. When the resectability rate is calculated from only the number of patients on whom operation was performed, namely 6,242, it is found to be 44.4 per cent. The resectability rate is important because even though the surgical rate may be high or may gradually increase as time goes on, this change does not mean that the ultimate results actually are being improved unless the resectability rate continues

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From the Division of Surgery, the Mayo Clinic.

1. Livingston, E. M., and Pack, G. T.: *Treatment of Cancer and Allied Diseases*. New York, Paul B. Hoeber, Inc., 1940, vol. 2, chap. 69, pp. 1110-1263.
2. Walters, W.; Gray, H. K., and Priestley, J. T.: *Carcinoma and Other Malignant Lesions of the Stomach*, Philadelphia, W. B. Saunders Company, 1942.



to be high. For only then will the actual percentage of cases in which resection is performed be increased.

In this series the mortality rate for all types of gastric resection was 16.2 per cent. This means that only 2,322 of the 2,772 patients who underwent resection actually survived the immediate postoperative period and therefore had a definite opportunity for ultimate cure. Thus, of the original group of 10,890 cases in which the diagnosis was established, 2,322 patients (21.3 per cent) were given a chance of cure. With improvement in operative technic, based on the original contributions of the pioneers in this field, advances in anesthesia and the improvements attained from close cooperation with colleagues in the medical services so that the patient might profit by their counsel, this mortality rate was reduced to 10.9 per cent for the years 1940 and 1941 together.

Of the patients who underwent resection and who survived the operation, 28.9 per cent lived five years or longer, 20.4 per cent lived ten years or longer, 15.2 per cent lived fifteen years or longer, 10.5 per cent lived twenty years or longer and 6.3 per cent lived twenty-five years or longer. Included in the calculation of these rates are all deaths, regardless of cause. The outlook at present for a patient with carcinoma of the stomach is illustrated in a general way in chart 1. Survival

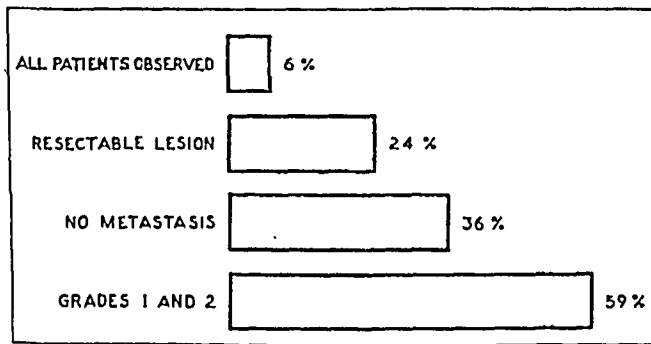


Fig. 1.—Five year survival rates of patients with resectable lesions, those with no metastasis and those with carcinoma of grade 1 or 2, compared with the five year survival rates of all patients observed who had carcinoma of the stomach (from Walters, Gray and Priestley<sup>2</sup>).

percentages depend largely on three important factors: surgical rate, resectability rate and operative mortality rate.

In the individual case many circumstances, as revealed by the history, physical examination and laboratory data, are concerned in the decision as to whether operation can be performed. In our large series the average surgical rate was 57.3 per cent. This has risen slightly in recent years at the clinic to 66.0 per cent in 1942. Similarly, numerous factors determine the resectability rate. Some of these are the surgeon's skill and experience, the patient's age and sex, the type of symptoms and their duration, gastric acidity, presence of a palpable mass, location of the lesion, extension to the neighboring structures and grade of malignancy. In the experience with the large series, as mentioned before, the resectability rate calculated on the basis of all cases in which the diagnosis originally was made was 25.5 per cent, and when figured from the number in which operation was performed, was 44.4 per cent. It is particularly interesting to note the rather remarkable increase in the surgical and resectability rates in the past year. Although the exact figures are not yet available for the year 1942, approximately 420 patients were seen whose condition was diagnosed as carcinoma of the stomach. The lesion in 143 (34.0 per cent) of these cases was thought to be inoperable and in 277 (66.0 per cent)

operable. In the latter group, the carcinoma in 123 cases (44.4 per cent) was found to be inoperable, and in 154 (55.6 per cent; 36.6 per cent of the entire series) resection of the stomach was performed. The reason for this increase in the surgical and resectability rates is not readily apparent but can be traced probably to the fact that the average lay person finally has become aware of the seriousness of persistent distress referable to the stomach and has sought professional advice at a period when the growth was still small enough so that resection could be performed before metastasis had occurred. The fact that a greater number of persons are working during the war also may play an important role, for the

TABLE 1.—Five Year Survivals After Resection for Carcinoma of the Stomach According to Grade of Malignancy

Grade	Patients			
	Who Survived Operation *		Who Lived 5 or More Years †	
	Total	Traced	Traced	Per Cent ‡
1.....	59	59	25	56.2
2.....	199	187	110	58.8
3.....	316	315	95	30.2
4.....	270	266	62	23.3

\* Inquiry as of Jan. 1, 1940. Included here are patients operated on five or more years prior to time of inquiry, that is, 1934 or earlier. Hospital mortality is excluded in the calculation of survival rates.

† Lived five or more years after leaving the hospital.

‡ Per cent of traced patients.

TABLE 2.—Five Year Survivals After Resection for Carcinoma of the Stomach According to Grade of Malignancy and Involvement of Lymph Nodes

Regional Lymph Nodes	Patients			
	Who Survived Operation *		Who Lived 5 or More Years †	
	Total	Traced	Traced	Per Cent
Not involved.....	919	912	593	43.1
Grades 1 and 2.....	167	165	110	66.7
Grades 3 and 4.....	244	241	104	43.2
Ungraded.....	568	506	179	35.4
Involved.....	1,049	1,039	171	16.5
Grades 1 and 2.....	52	51	25	49.0
Grades 3 and 4.....	342	340	53	15.6
Ungraded.....	655	648	93	14.4

\* Inquiry as of Jan. 1, 1940. Included here are patients operated on five or more years prior to the time of inquiry; that is, in 1934 or earlier. Hospital mortality is excluded in the calculation of survival rates.

† Lived five or more years after leaving the hospital.

former financial barriers to adequate medical examination in many instances now have been removed.

All patients for whom resection of the stomach for gastric carcinoma has been performed but who do not survive the operation have been denied the possibility of cure just as definitely as those on whom operation has not been performed. Thus, the third important factor that influences the prognosis for the patient with this lesion is the operative mortality rate. The various factors which influence the operative mortality rate do not come rightly within the scope of this paper. Some, however, may be mentioned. Among the more important are: judicious preparation to correct dehydration, chemical imbalance and anemia; selection and skilful administration of the anesthetic agent; the type of operation employed and the degree of difficulty encountered; the skill of the surgeon; the

size of the lesion and the extent of invasion of adjacent tissues; the age and sex of the patient, and the postoperative care.

Other factors influence survival following successful gastric resection. One of these is the grade of malignancy according to Broders' method of identification. In our large group of cases it was observed that the lower the grade of malignancy of the lesion the better the prognosis and conversely the higher the grade of malignancy the worse the prognosis. This is clearly shown in table 1.

Next to the grade of the malignancy the presence or absence of involvement of regional lymph nodes was found to be of greatest significance (table 2). When resection was performed in the absence of involvement of regional lymph nodes, the five year survival rate was 43.1 per cent, as contrasted with only 16.5 per cent when regional lymph nodes were involved. The importance of removing all regions of lymphatic drainage from the stomach as completely as possible whenever gastric resection is performed is apparent and should include in every case all of the greater omentum.

If the regional lymph nodes were not involved but if the growth had extended to certain neighboring structures, the five year survival rate following removal of the growth and its extension was approximately 5 per cent less than in cases in

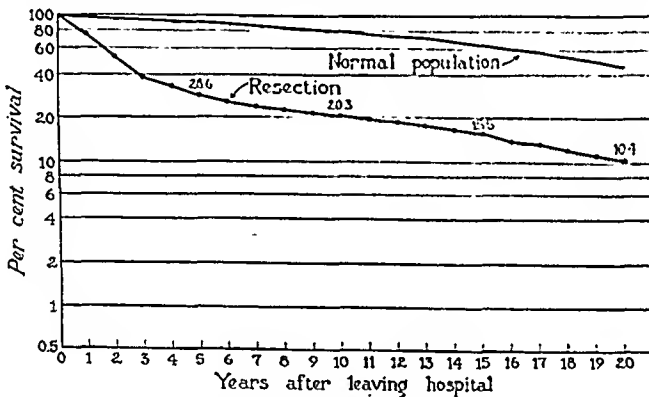


Fig. 2.—Survival rates for twenty years of patients who had had resection of the stomach for carcinoma compared with those of the normal population (from Walters, Gray and Priestley<sup>2</sup>).

which such direct extension did not exist. Thus it would appear that invasion of the adjacent lymphatic structures is of more significance as regards prognosis than is direct extension of the lesion, provided, of course, that the entire lesion can be removed. Experience has shown, however, that extragastric extension does not contraindicate resection. When the primary lesion has been removed in cases of carcinoma of the stomach, the extragastric extensions sometimes may resolve spontaneously. This same course obtains on removal of the primary lesion in other locations.

The size of the lesion which was resected was not found to bear any direct relationship to the survival rates following resection. However, the site of the lesion in the stomach was found to be of some significance. In general, lesions on the lesser curvature gave a somewhat better prognosis than those situated on the greater curvature. Lesions situated in the middle portion of the stomach afforded a greater opportunity for cure following resection than those located in either the pyloric or the cardiac portion.

The survival curve for patients with carcinoma of the stomach for a period of twenty years after their leaving the hospital is shown in figure 2. It is interesting

to note that five to seven years subsequent to resection the survival rates for the patients who had undergone resection for gastric carcinoma were similar to those for the general population of comparable age. This evidence substantiates the term "five year cure", because if a patient lived five or more years after resection his chance of survival during the ensuing years was just about the same as it would have been for any person of his age in the general population. Also included in chart 2 are the survival rates for those patients on whom either a palliative operation or exploratory laparotomy alone was carried out.

#### SUMMARY

In a series of 10,890 cases of carcinoma of the stomach, slightly more than half the patients (57.3 per cent) seen clinically in the Mayo Clinic from 1907 to 1938 inclusive were considered to be in the operable stage of the disease. This number has risen in recent years to about two thirds (66.0 per cent) in 1942. Approximately half of these patients (25.5 per cent of the large series and 36.6 per cent in 1942) were found to have removable lesions at the time of exploratory laparotomy.

The average hospital mortality rate in this series of 10,890 cases for all types of resections of the stomach for carcinoma was 16.2 per cent, but for the years 1940 and 1941 together the hospital mortality rate was 10.9 per cent. Of those patients who underwent resection and survived the immediate postoperative period, 28.9 per cent were alive at the end of five years and 6.3 per cent lived twenty-five years or longer.

In this group of cases it was observed that the lower the grade of malignancy according to Broders' method of identification, the better was the prognosis, and, conversely, the higher the grade of malignancy the worse was the prognosis. Eighty-six and two tenths per cent of the patients who had carcinoma of grade 1 were alive five years after resection, whereas only 23.3 per cent of these patients who had carcinoma of grade 4 were living after a comparable period.

From the prognostic standpoint, the presence or absence of involvement of the regional lymph nodes was of the greatest significance. In cases in which the regional lymph nodes were not involved, the five year survival rate was 43.1 per cent, as contrasted with only 16.5 per cent in cases in which the regional lymph nodes were involved.

If a patient lived five or more years after resection of a carcinoma of the stomach, the chance of survival during the ensuing years was found to be about the same as it is for any person of comparable age in the general population.

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